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REVIEW ARTICLE

Flowchart for early diagnosis, treatment and monitoring of iron deficiency for children

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Abstract

Iron deficiency anemia is defined as a hemoglobin concentration less than a second standard deviation from the distribution mean for a population of the same sex and age. It is the last event in a progression of negative iron balance, with the stages: negative balance, iron deficiency, and iron deficiency anemia. It is the most common hematologic alteration in the world, especially in developing countries. The main source of iron in the body comes from the red blood cell recycling system, while a smaller portion comes from the diet. Despite this, nutritional deficiency is the main etiology of iron deficiency anemia and iron deficiency in childhood. Iron is essential for several physiological functions and its deficiency, especially in childhood, can compromise mental and physical development. Clinical manifestations usually become detectable in severe deficiency. For this reason, the early diagnosis of iron deficiency is through laboratory tests. It should be performed through screening at 12 months of life. Treatment should be started promptly after diagnosis. Diet is of little value in correcting iron owing to the low bioavailability of iron in most foods. However, preparations containing iron are easily absorbed by the body. Given the severity of this condition, treatment should be monitored using laboratory parameters. This study aims to develop a protocol for screening and monitoring the treatment of iron deficiency anemia to systematize and organize care, bringing better results for the childs development.

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INTRODUCTION

Anemia is a condition in which the hemoglobin concentration is below the second standard deviation of the distribution mean of its reference value for a population of the same sex and age, living at the same altitude[1]. With a decrease in hemoglobin levels, the transport of oxygen to tissues is impaired, affecting the functioning of the body in affected individuals[2].

Iron deficiency anemia occurs when there is an imbalance between the absorption of iron or its elimination and the organic needs for this mineral, being the most serious form of iron deficiency[1].

This metal is vital for the function of a wide variety of enzymes, such as catalases, reductases and peroxidases, which depend on the properties of iron to carry out chemical reactions essential for survival. Furthermore, the body depends on hemoglobin, a protein that contains iron, to transport inhaled oxygen from the lungs to peripheral tissues[3]. Human existence is dependent on iron, and its deficiency can compromise a child's mental, cognitive and physical development, in addition to reducing resistance to infections, resulting in an increased frequency of illness[4].

It constitutes a common childhood condition, especially in the context of social and economic helplessness, generating its main etiology, which is nutritional deficiency. However, it may be associated with genetic diseases, infections, use of specific medications that prevent or impair iron absorption[5].

Iron deficiency is the most common blood alteration, both in developed and developing countries[3]. Approximately 10% of the world's population has this deficiency[6].

In Brazil, it is a common nutritional problem that mainly affects children, women of childbearing age and pregnant women[5]. Data from the National Demographic and Health Survey of August 2022 found that 20.9% of children under 5 years of age had the disease[6]. In the northeast and north regions of the country, the prevalence of this anemia in children reaches a percentage of more than 53%[7]. Although the prevalence of this disease was still high in 2020, this rate has been decreasing in recent years. For our association (SBP), the main causes of this reduction were the increase in the prevalence of breastfeeding, use of enriched formulas, improved access to food sources, government and private educational campaigns, in addition to environmental changes[7].

Due to its high prevalence in children, iron deficiency anemia becomes a serious condition as it has an effect on the growth and development of almost an entire generation of a population at risk, especially in children who are poorly stimulated or of low social and economic status. The condition can affect physical and brain development throughout life, if not reversed through supplementation, especially in the first thousand days of life, moments of maximum development[8]. Despite the implementation of public policies for prevention and treatment, it is still a major public health challenge in Brazil[8].

Iron deficiency is generally asymptomatic, with symptoms more noticeable in later stages, such as in already established iron deficiency anemia. It can manifest with fatigue, dizziness, paleness and headache. However, its long-term consequences are of greater importance, as it can result in sequelae in the cardiovascular, neurological and immunological systems, and can irreversibly affect cognitive, auditory, motor and visual functions[4].

Studies show that iron deficiency since the prenatal period, when present in the mother, has important and long-term deleterious repercussions on the development of children's cognitive, behavioral, language and motor skills[9], and the possible negative impact remains even after early treatment for decades. Maternal anemia influences the infant's hemoglobin values up to 6 months of age, even with exclusive breastfeeding, data shown in national surveys[10].

Given the relevance of the topic addressed, it is essential that healthcare professionals are trained to guide caregivers, carry out prophylaxis efficiently, carry out screening, initiate treatment, when necessary, evaluate response to treatment and intervene precisely. This review addresses this topic of great relevance to public health and establishes a screening protocol for iron deficiency anemia and monitoring of previously healthy patients, in addition to evaluating the response to treatment in a systematic way so that care is organized and the result is more effective. In this way, quality childcare is promoted, ensuring that children grow up to the maximum of their physical and mental capabilities.

Iron Homeostasis

Among the metals present in the human body, iron is the most abundant[7], with a total of approximately 4 grams distributed as follows:

1) Red blood cells (largest portion, around 70-75%, linked to the heme of hemoglobin);

2) Iron storage compartments (25% of the total, represented by ferritin and hemosiderin proteins present mainly in cells of the intestinal mucosa, macrophages of the spleen and bone marrow);

3) Circulating in plasma, bound to serum transferrin (about 2%).

Apoferritin, hemosiderin and transferrin are proteins capable of binding iron, found in plasma and intracellularly.

Apoferritin is a protein synthesized by the liver (a type of "acute phase reactant" protein). It has a structure capable of storing iron atoms, and, when linked, it is called ferritin. This protein is mainly responsible for iron storage in the body. Its serum concentration varies directly proportional to iron reserves. Normal plasma ferritin levels range from 20 to 200 ng/ml. Each ng/ml of serum ferritin corresponds to 10 mg of stored iron.

Most of the iron used in the human body comes from the red blood cell recycling system itself through destruction by spleen macrophages. The other small part is acquired through diet.

There are two forms of dietary iron: (1) ferrous iron or heme iron; is the most easily absorbable form of iron, coming from the heme ring present in red meat, mainly offal, poultry meat, pork, fish and shellfish and (2) ferric iron or non-heme iron, being the least absorbed form, present in leafy vegetables dark green vegetables and legumes, such as beans and lentils. [11]. This ability to exist in either the stable Fe^{2}+ (ferrous) or Fe^{3}+ (ferric) oxidation states gives this metal its broad biological utility[12].

Non-heme iron is intensely influenced by nutritional factors in its absorption process, while heme iron has independent regulation that does not vary with diet[7]. Foods such as meat proteins, vitamin C, other organic acids (citric, malic) stimulate absorption; while phylates (present in fiber and cereals), minerals (potassium, zinc, copper, magnesium), egg proteins (albumin) and milk (casein), phosphates (present in milk and eggs) and phenolic compounds (black tea, mate, soft drinks and coffee) inhibit them.

Gastric acidity is responsible for food emulsification: hydrochloric acid solubilizes iron salts and maintains Fe^{2}+ in the ferrous form. This is absorbed in the small intestine. In plasma, iron binds to plasma transferrin and is transported through the blood until it finds receptors on the membranes of erythroblasts in the bone marrow.

In iron deficiency anemia, some changes in homeostasis occur. The iron absorption capacity of the intestine can be increased by up to five times normal. Transferrin has a significant increase in its avidity for iron (reflecting an increase in its iron binding capacity or TIBC), but with low saturation, with a reduction in the transferrin saturation index (TSI). Deficiency also reduces hepcidin production, which leads to increased iron availability.

Stages of iron deficiency

Iron deficiency anemia is the last event that occurs in the progression of negative iron balance in the body[5]. There are three stages to its development:

First stage: iron depletion. The demand for iron is greater than the absorption capacity or availability of this element in the body. In this way, body stores are mobilized in the reticuloendothelial system, causing a decrease in the fraction of iron and ferritin in the bone marrow. Laboratory findings at this stage are normal serum iron, protoporphyrin, TIBIC, hematimetric indices and low ferritin. In the bone marrow, iron and ferritin are low. The subsequent stage begins when endogenous iron stores reach a very low limit (by definition, ferritin lower than 12µg/L is a strong indicator of depletion of body iron reserves for children under 5 years old, and lower than 15µg/L for children between 5 and 12 years old).

Second stage: Iron deficiency. With depleted stores, serum iron begins to decrease, TIBC rises, and TSI gradually decreases. Thus, hemoglobin and hematocrit begin to fall, normocytic and normochromic anemia is detected and the erythrocyte production rate is reduced. There may be thrombocytosis due to hyperstimulation of the bone marrow. RBC progenitor cells in the bone marrow are large and normally divide several times to produce smaller mature cells, justifying the increased level of anisocytosis.

Third stage: Iron deficiency anemia. As the second stage worsens, hypochromia and microcytosis become evident and, in more advanced stages, microcytic anemia with ferritin below 15 µg/mL, transferrin saturation less than 15%, serum iron below 30 mcg/dL, elevated RDW and low hemoglobin levels.

Etiology and risk factors

Iron deficiency anemia can be secondary to deficiency in the production, destruction of red blood cells or resulting from blood loss[5]. There are multiple factors, both biological and social, that can influence the progression of the condition.

Inadequate diet in qualitative or quantitative terms is the main factor that causes iron deficiency anemia. In quantitative terms, populations with nutritional deficiencies stand out; with inadequate iron intake.

Other causes are vegetarian habits, diets with excess tea or coffee, which inhibit the absorption of iron, or diets without vitamin C (citrus fruits), which favor its absorption.

Blood loss may be due to the presence of endemic infestations (malaria, ascariasis, intestinal protozoa), or intestinal malformations, such as Meckel's diverticulum, present in 2 to 4% of the general population[5,13]. The use of cow's milk is associated with the loss of occult blood in the feces in 30% of cases (entero-proctocolitis due to cow's milk allergy).

An important risk factor for iron deficiency anemia is low birth weight (less than 1,500 g) and prematurity. Prolonged feeding only with breast milk (more than six months) can also be associated with iron deficiency, anemia and micronutrient deficiencies[4]. especially in premature babies[14].

The update from the Brazilian Society of Pediatrics (SBP)[15] of August 2021 established specific risk factors that must be evaluated when deciding on the start and dose of iron deficiency anemia prophylaxis. They are described in Table 01.

Repercussions of anemia in a child's health

The majority of cases are asymptomatic, and the symptoms can only be recognized once the iron deficiency has been resolved, and they have effective physical normality to compare with their previous state.

Furthermore, systemic manifestations of iron deficiency anemia will generally only be present in severe anemia. Despite this, some patients with low ferritin and no anemia may have the same symptoms[4].

Among the manifestations, changes in nails and epithelium stand out, such as paleness of the face, palms, the conjunctiva and oral mucosa, alopecia, brittle and rough nails, koilonychia and angular stomatitis.

Highlights in the gastrointestinal system include reduced gastric acidity, atrophic gastritis, bleeding of the intestinal mucosa and pica (a perverted appetite for foods with low

Table 1. Main risk factors for iron deficiency anemia for children and adolescents according to the SBP in 2021.

Low maternal reserve
- Multiple gestations with short intervals among them - Iron-deficient maternal diet - Blood losses - No iron supplementation during pregnancy and breast feeding
Increased metabolic demand
- Prematurity and low birth weight (< 2,500g) - Rapidly growing infants (growth velocity > p90) - Girls with large menstrual losses - Competition athletes
Reduction in supply
- Umbilical cord clamping before one minute of life - Prolonged exclusive breastfeeding (more than six months) - Complementary feeding with foods poor in iron or with low bioavailability of it - Consumption of cow's milk before one year of age - Consumption of infant formula with low iron bioavailability - Vegetarian diets without guidance from a doctor/nutritionist - Absence or low compliance to prophylactic supplementation with supplement iron, when recommended
Blood loss
- Traumatic or surgical - Gastrointestinal bleeding (e.g. inflammatory bowel disease, colonic polyposis, non-steroidal anti-inflammatory drugs, Helicobacter pylori infection, verminosis – strongyloidiasis, helminthiasis, ancylostomiases – allergic enteropathies/colitis, schistosomiasis) - Gynecological bleeding (menorrhagia, intrauterine devices) - Urological bleeding (schistosomiasis, glomerulonephritis, renal trauma) - Pulmonary hemorrhage (tuberculosis, lung malformation, idiopathic pulmonary hemosiderosis, Goodpasture syndrome, etc.) - Blood dyscrasias - Malaria
Iron malabsorption
- Malabsorption syndromes (celiac disease, inflammatory bowel disease) - Atrophic gastritis, gastric surgery (bariatric, gastric resection) - Reduction of gastric acidity (antacids, H2 blockers, proton pump inhibitors)

Legend: Main causes of iron deficiency anemia.
Brazilian Society of Pediatrics 2021[16]

nutritional value, such as starch, earth or ice; the latter is considered specific for iron deficiency). There may be complaints of pain in the tongue, dry mouth due to decreased salivary flow and atrophy of the lingual papillae[4].

It also affects the psyche, generating anorexia, irritability, conduct and perception disorders, psychomotor disturbance.

It alters immunity by inhibiting the bactericidal capacity of neutrophils, it decreases T-lymphocytes, predisposing to infections and may perpetuate the anemia process.

In daily activities, there is decreased work capacity and exercise tolerance, asthenia, wheezing and pain in the lower limbs[16].

The condition also predisposes to dental cavities, reduces odor discrimination, causes changes in the response to metabolic stress and audiovisual development[7].

Iron deficiency anemia is also responsible for lower scores on mental development tests when compared to people without the condition with better iron status, in addition to emotional difficulties, disadvantages in relation to breastfeeding and family experiences[3]. Studies have shown that the cognitive deficit is greater in these patients and was not reversed with early supplementation for short periods (30 days). A minimum of 90 days is required for modest positive effects to appear in the depletion of iron stores with full patient compliance. The ideal would be prolonged intervention times, depending on the salt used[17].

When present during pregnancy (especially in the first and second trimesters) it is associated with risk outcomes for the child, such as prematurity and low birth weight. Furthermore, in the postpartum period, it can intervene in the care of the newborn and its development, because it causes a reduction in the quality of life of the nursing mother and an increase in the prevalence of depression, also impairing breastfeeding[7].

Differential diagnosis

In the differential diagnosis, other causes of microcytosis must be considered, such as alpha and beta thalassemia and anemia of inflammation and/or chronic parasitic diseases, such as malaria and schistosomiasis. (7) Other nutritional causes must be investigated, such as folic acid deficiency generating

macrocytosis, vitamin A and vitamin B12 deficiency. Lead poisoning can also generate a similar situation, and a high protoporphyrin dosage can help in the differential diagnosis. Sideroblastic anemia should be considered when there is known family history, clinical features that suggest a syndromic condition, or lack of another diagnosis.

For cases not resolved with usual treatment, other tests can be used, such as measurement of serum iron, transferrin, erythrocyte zinc protoporphyrin, total iron binding capacity, among others.

A heel prick test (neonatal screening) may be used to rule out genetic causes of anemia and hemoglobinopathies[8].

Diagnosis

The diagnosis is based on the findings of laboratory tests. If iron deficiency anemia is suspected, the blood count (with hematimetric indices) and peripheral smear are of great value, but the "iron screening" (serum iron, serum ferritin and TIBIC) will be more useful for diagnostic confirmation. The blood count and ferritin should be requested together since although hemoglobin is used to assess anemia, it has low specificity and sensitivity, with ferritin being a more reliable biomarker of iron status[18]. In doubtful cases, bone marrow aspirate (myelogram) stained with Prussian blue can be used for confirmation.

Serum ferritin concentration can replace previously performed bone marrow assessment. Normal values are 40 to 200 ng/mL (mcg/L), and it is a very rare clinical situation in which low levels do not mean iron deficiency. Therefore, any individual with a ferritin concentration lower than 10 to 15 ng/mL can be considered iron deficient.

As it is an acute phase marker, increasing its levels in inflammatory, infectious, malignant or hepatic diseases, there may be situations of up to a three-fold increase in ferritin in the presence of these conditions, concomitant with iron deficiency anemia. Therefore, in these patients it is suggested to reduce the ferritin value by the 3rd part and interpret values less than or equal to 20 ng/mL suggestive of anemia due to concomitant iron deficiency.

Other measurements, such as total iron, transferrin and transferrin saturation are not mandatory, but can help in the investigation.

Specific laboratory tests show a diagnosis in each of the iron deficiency stages[19].

In the first stage, iron depletion, there is a decrease in iron deposits in the liver, spleen and bone marrow, which can be seen from serum ferritin. When lower than 12µg/L, it is a strong indicator of body iron reserves depletion in children under 5 years of age, and lower than 15µg/L for children aged 5 and 12 years[8].

In the second stage, iron deficiency, reduced serum iron is evidenced, associated with increased total transferrin binding capacity (>250-390µg/dl), reduced transferrin saturation (<16%), and reduced transferrin. Erythrocyte zinc protoporphyrin and total iron binding capacity can also be measured. Serum iron is considered in this diagnosis when its values are lower than 30 mg/dl[8].

The third stage, iron deficiency anemia, is the final stage of iron deficiency. Once anemia sets in, low levels of hemoglobin initially appear, being normocytic (mean corpuscular volume - MCV – normal), normal reticulocytes and low iron status markers (lower ferritin, iron, ferropexic capacity, transferrin and IST). As the process continues, hypochromic anemia (with medium corpuscular hemoglobin) and microcytosis (with low MCV) will appear. As the condition worsens, anisocytosis appears (cells of varying sizes) and, upon hematoscopy, poikilocytosis (cells of varying shapes)[21].

According to the WHO, the cutoff points for diagnosis are hemoglobin values below 11g/dl for children aged 6 to 60 months and 11.5g/dl for children aged 5 to 11 years. In relation to hematocrit, values below 33% are considered inadequate for children aged 6 to 60 months, and 34% for those aged 5 to 11 years. Currently, the use of variations in hemoglobin levels according to age is determining, with acceptable ranges[22]. The normal value of the erythrocyte series varies in children with age and sex; therefore, for the diagnosis of anemia, the values already defined in the scientific literature should be consulted[7].

The laboratory diagnosis is not pathognomonic and must be analyzed through combinations of different tests and their interpretation in conjunction with the clinic[7].

Only if, after laboratory investigation, there are still doubts regarding the diagnosis, bone marrow aspirate (myelogram) can be used. This test is the most accurate for diagnosing iron deficiency anemia.

Iron deficiency anemia screening

Clinical evaluation in iron deficiency anemia is not sufficient for early diagnosis, as manifestations become detectable in an already established condition or severe deficiency. This situation already poses a risk to the child's full development.

Early detection of anemia in childhood is urgent so that treatment can be initiated promptly and must be carried out through laboratory examination.

The consensus proposal is that there should be screening tests for children around 12 months of age. However, in cases of suspicion based on the presence of risk factors, investigation must be carried out early, especially in the absence of adequate iron prophylaxis[21].

The routine laboratory tests recommended by the consensus are preferably a complete blood count (with hematimetric indices), study of red blood cells morphology, reticulocyte count and ferritin.

CRP measurements are also proposed to rule out inflammatory and infectious processes that could interfere with ferritin values.

In the depletion phase, ferritin is the marker, and it is known that when there is intervention in this phase, the results are possible prophylaxis of cognitive deficits. For consensus,

ferritin must have values above 30µg/dl. Values lower than 15µg/dl indicate severe deficiency and intermediate values should be evaluated after iron supplementation.

The diagnosis of anemia by hemoglobin value must be made based on normal ranges (for age and sex) and not by absolute value[7].

Children under one year of age who receive fresh cow's milk or inadequate formula constitute a nutritional risk situation for iron deficiency anemia and should be assessed early regarding the need for treatment[7].

Treatment

Dietary therapy is of no value when used alone to correct iron deficiency anemia due to the low bioavailability of iron in foods. On the other hand, preparations containing iron in the ferrous form (Fe^{2}+) are easily absorbed by the body.

Once the diagnosis of iron deficiency anemia has been established, treatment must be started urgently, with the best salt available, with adequate control and for the necessary time, associated with non-drug treatment[7]. Even without a confirmed diagnosis, the presence of mild microcytic anemia in children with a presumptive diagnosis of iron deficiency anemia, the best approach is to give iron empirically and evaluate the response[4].

It is important to resolve underlying diseases that may be associated with the iron deficiency anemia.

The objective of treatment is to improve symptoms, followed by recovery of hematological parameters and iron biomarkers[4].

Non-drug treatment

A diet with good sources of iron must be guaranteed.

As already mentioned, there are two types of iron in foods, heme iron (animal origin, being better absorbed) and non-heme iron (found in vegetables).

To enhance iron absorption, it is recommended to simultaneously consume foods rich in vitamin C, available in citrus fruits.

Drug treatment

Iron replacement should be done with elemental iron at recommended doses of 3 to 6 mg/kg/day, depending on the severity, for a minimum of eight weeks. Generally, 3 mg/kg is recommended once or twice a day, with a maximum of 150 mg of elemental iron per day. Within 4 weeks, hemoglobin should rise more than 1 g/dL. Supplementation should be continued to replenish iron stores, which should vary from two to six months or until serum ferritin is greater than 15µg/dL, but ideally between 30 and 300µg/dL and improvement in symptoms[7,4].

Iron supplementation is associated with adverse effects that can render treatment ineffective as they are poorly tolerated. These effects are overcome when the medication is administered with meals[4]. However, the absorption of ferrous sulfate is better when administered on an empty stomach. They should also not be taken with antacids, proton pump blockers, drinks and supplements with calcium, antibiotics (quinolones and tetracyclines), coffee, tea, milk or eggs, which also reduce their availability.

However, this measure is flexible in order to improve patient compliance and make oral treatment effective. Doses can be taken with meals, divided or even reduced to alleviate adverse effects. It is essential to motivate compliance, with educational messages and information on the benefits of treatment for caregivers[4]. Therapeutic improvement must be monitored, as the absorption of elemental iron becomes reduced with the alkaline pH of foods.

Consensus recommendations on iron deficiency anemia recommend early treatment for a minimum period of two months of adequate use of iron (a minimum of three months is suggested to replenish reserves)[7].

As important as preventing iron deficiency in childhood is, attention should also be paid to the risks of iron overdose. It is known that the intestine only absorbs a number of the nutrients that pass through it, and an overdose of iron reduces the absorption of other elements such as zinc and copper, which creates other risks to a child's development[22]. Furthermore, the oxidation of ferrous iron generates free radicals, and excessive iron absorption increases the saturation of transferrin and free iron in plasma, which is toxic to the body[7]. The maximum recommended dose of iron is 150 to 200 mg of elemental iron per day, in two or three doses[23].

Types of iron available for supplementation

There are several types of iron salts for supplementation. Among them, ferrous salts, aminochelated iron, polymaltosed iron complex (ferripolymaltose) and carbonyl iron stand out[7]. It is important that the doctor is aware of the exact amount of elemental iron in the compound he is prescribing for the treatment of his patient. Table 2 summarizes the amount of elemental iron per drop for each type of presentation.

Table 2. Amount of elemental iron in each type of iron saltq.

Type of iron	Elemental iron per pill	Elemental iron in liquid form
Ferrous sulphate	40-60	Each drop equals 1.25 mg of elemental iron Each 1 mL of the syroup has 8 mg of elemental iron
Ferripolimaltose (may have two forms, read the insert)	100	Each drop has 2.5 to 5 mg of elemental iron. Each 1 mL of the syroup has 10 mg of elemental iron
Aminochelate iron	30 a 100	Each drop has 2.5 mg of elemental iron
Carbonyl iron	120	Each drop has 2.5 mg of elemental iron

Source: Cançado (2009)[24].

All iron compounds have similar efficacy in treating and preventing iron-deficiency anemia.

Ferrous sulfate is effective in correcting anemia and replenishing iron stores, it has low cost and rapid absorption (active and passive diffusion in the duodenum) (23). Each 1 mg of ferrous sulfate is equivalent to five times the amount of elemental iron in mg. However, it is influenced by dietary components and supplementation should be taken away off meals, recommending taking it on an empty stomach, 1 hour before meals or before bed[7].

Regarding adverse effects, they are present in 35% to 55% of children who use ferrous salts[23].

Ferric salts (ferripolymaltose) can be administered during or after a meal and it carries a lower incidence of adverse effects, which gives them greater compliance and better treatment results[23].

Other options are ferrous salts with aminochelated iron (covalent union of iron in ferrous form chelated with an amino acid glycinate and calcium citrate) and carbonyl iron[23].

Treatment monitoring

ith established therapy, a feeling of well-being is noted in the first days of treatment along with the disappearance of more intense symptoms, such as pica or restless legs syndrome. During this period, there can also be a discrete reticulocytosis, peaking between 5-10 days. Hemoglobin rises slowly within one to two weeks, reaching an increase of 2 g/dL in three weeks. Within four weeks, the deficit decreases by 50% and tends to normalize within six to eight weeks if there is no blood loss. Clinically, the lingual papillae are progressively reconstituted over weeks to months. Iron stores are reestablished within six months of treatment. The objective is to keep patients in their normal activities, minimizing the adverse effects of the medication in use as much as possible[4].

Given the severity of iron deficiency, treatment must be systematically monitored. It must be carried out using laboratory parameters of reticulocytes, complete blood count, every 30 to 60 days, and measurement of iron stock markers (ferritin), at 30 and 90 days. Treatment should last until iron stores are replenished, almost always around six months[7].

Treatment failures

The main cause of treatment failure is inappropriate use of the medication, which may be due to poor treatment compliance due to gastrointestinal adverse effects, inadequate dose or insufficient duration. Other important causes are continued blood loss (due to failure to identify bleeding or iron absorption disorder, such as celiac disease, atrophic gastritis, comorbid diseases that interfere with the response to oral iron), anemia, chronic disease, chronic kidney disease , associated inflammatory or infectious disease, misdiagnosis (such as beta thalassemia minor), and combined nutritional deficiencies[23].

Flowchart for early diagnosis, treatment and monitoring of iron deficiency anemia

The following flowchart systematically establishes the early diagnosis, treatment and monitoring of iron deficiency (image 1).

Prevention

These are measures to prevent anemia at a collective level that must be prioritized through public policies and reviewed by healthcare professionals frequently, paying attention to the updates mentioned in Chart 1:

An also very important measure, due to its great prevalence in our environment, is to advise against consuming fresh and unprocessed cow's milk, in powder or fluid form, until 12 months of age, and, after this period, limiting consumption of 500ml per day[7].

Since 2005, in Brazil, there have been policies for iron supplementation, the National Iron Supplementation Program (PNSF). The PNSF encompasses infants aged six to 24 months, pregnant and lactating women up to the third month postpartum, recommending prophylactic supplementation with oral iron salts. According to the program, infants between six and 24 months old must be supplemented with iron at a dosage of 1mg per kilogram of weight per day[11].

Currently, the Brazilian Society of Pediatrics advises infants on exclusive breastfeeding, without risk factors already mentioned in this paper, to start prophylactic iron supplementation from 180 days of life, until the end of the second year. In those with risk factors, supplementation should be started at 90 days, regardless of the type of diet. For premature newborns (gestational age less than 37 weeks) or those weighing less than 2,500g, the start should be at 30 days[23]. The recommendations from SBP, SPSP and the PENSI Institute in 2021 for prophylactic iron supplementation are depicted on table 03.

Final remarks

Even though it affects all age groups, ethnicities and social layers, iron deficiency anemia is still a disease that primarily affects the socially less favored, lower income and low development groups. This fact becomes even more socially unfair given current studies that show that children suffering from iron deficiency are already at lower levels of cognitive capacity when compared to groups without disabilities, even when social and economic levels are matched. With treatment, there is cognitive improvement, but it is not comparable to the control group without iron deficiency. Long-term follow-up shows results with behavioral deficits, increased risk of violence, and social difficulties, even after 20 years of treatment. The sequelae are more important the lower the degree of stimulation and the lower the patient's social and economic level.

Given this situation, it is clear that prophylaxis and early identification of iron deficiency anemia is a true pediatric emergency and a public benefit action that can change the lives of an entire generation.

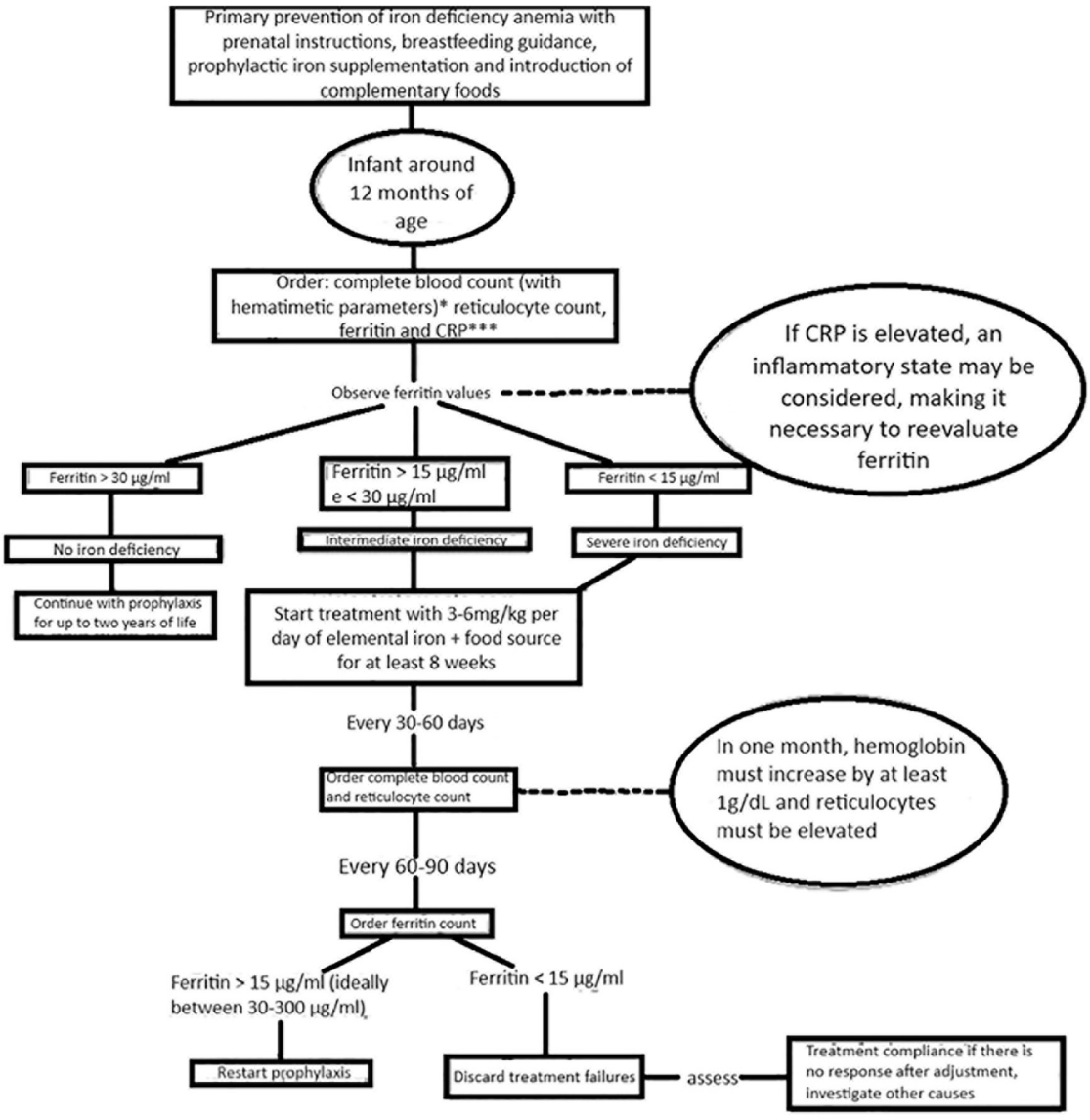


Image 1. Flowchart for early diagnosis, treatment and monitoring of iron deficiency.
Source: own authorship.

Chart 1. Collective measures to prevent iron deficiency anemia in children.

- Breastfeeding;
- Prophylactic supplementation;
- Fortification of food and meals (it is suggested to evaluate the effectiveness of the program at current dosages);
- Reinforcement of pediatric consultation during prenatal care;
- Encouragement of neonatal screening tests to analyze other causes of anemia;
- Adequate clamping of the umbilical cord after birth;
- Appropriate guidelines for complementary feeding of infants;
- Appropriate use of infant formulas;
- Nutritional guidelines suitable for families with specific eating routines (such as vegetarianism) or families whose children eat all their meals at school.

Table 3. Recommendation for prophylactic iron supplementation in infants.

Newborns WITHOUT RISK FACTOR, full-term, AGA, on EBF until the 6th month	1 mg of elemental iron/kg/day, starting at 180 days of life until the 24th month of life
Newborns WITH RISK FACTOR, full-term, AGA, on EBF until the 6th month	1 mg of elemental iron/kg/day, starting at 90 days of life until the 24th month of life
Full-term newborns, AGA, regardless of the type of feeding	1 mg of elemental iron/kg/day, starting at 90 days of life 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 life, for one year. After this period, 1 mg/kg/day for another year.
Premature newborns weighing more than 1,500 g	2 mg of elemental iron/kg/day, starting at 30 days of life, for one year. After this period, 1 mg/kg/day for another year
Premature newborns weighing between 1,500 and 1,000 g	3 mg of elemental iron/kg/day, starting at 30 days of life, for one year. After this period, 1 mg/kg/day for another year
Premature newborns weighing less than 1,000 g	4 mg of elemental iron/kg/day, starting at 30 days of life, for one year. After this period, 1 mg/kg/day for another year
Premature newborns who received more than 100 mL of packed red blood cells during hospitalization	They must be evaluated individually as they may not require iron supplementation at 30 days of age, but rather later.

Source: Brazilian Society of Pediatrics 2021[16]

Efforts and strategies to prevent iron deficiency must include poverty reduction, access to appropriate diets for each age group, improvements in health services and basic sanitation, and the promotion of better care with better eating practices. Preventive and sustainable treatment primarily includes ensuring the necessary nutritional supply of iron for the most vulnerable population and prophylaxis with oral iron.

In order for the diagnosis and treatment of iron deficiency anemia to occur as early as possible, cooperation and support from scientific or mixed societies is urgently needed in order to encourage pediatric prenatal consultation for adjustments in the assessment of maternal anemia and preventive/corrective supplementation. Anemia secondary to inadequate prenatal care, lack of breastfeeding or inadequate introduction of supplementary foods with good sources of iron are potentially preventable causes and are the responsibility and action of healthcare professionals in managing this major national health problem.

This study is of scientific and social importance, systematizing the approach to iron deficiency to facilitate and organize the fight against this condition, which is a true emergency in pediatrics.

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