



REVIEW ARTICLE

Determinant factors of anemia in children

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Abstract

Objective: to present a review about the main determining factors of anemia in children under 5 years old.

Source of data: information was used from articles published in indexed national and international scientific journals, technical books and publications from international organizations.

Synthesis of the data: anemia constitutes the world's nutritional problem of the greater magnitude, and children under 5 years old represent one of the highest risk population groups. As with any public health problem, the origin of anemia is multi-causal and thus in this article the attempt is to interpret its direct or indirect relation with possible determinant factors and the main concordant or discordant findings in epidemiological studies. Among these factors are the social and economic conditions, the conditions of child health care, the child's nutritional state, the presence of morbidity, food consumption and biological factors. The role of the diet is emphasized with respect to the consumption and bioavailability of iron, and age of the child as the main determinants.

Conclusions: bearing in mind the magnitude of the problem and the breadth of its risk factors reviewed in this study, the implementation of urgent prevention and treatment measures for iron-deficiency anemia becomes necessary. It is important to stress that a single strategy may have little success if other measures are not taken simultaneously; the role of nutritional education being relevant, together with other implemented actions. Children under 2 years old and children who live in rural and deprived areas should be priorities in programs to combat anemia.

J Pediatr (Rio J) 2002; 78 (4):269-78: anemia, hemoglobin, determinant factors, child.

Introduction

Nutritional anemias result from the simple or combined deficiency of nutrients, such as iron, folic acid and vitamin B12. Other rare types of anemia can be caused by deficiency of pyridoxine, riboflavin and protein. Although various nutrients and cofactors are involved in maintaining the

normal synthesis of hemoglobin, iron deficiency is the most frequent cause of anemia on a worldwide basis. This type of deficiency is the most widely spread, affecting especially children and pregnant women in developing countries.¹⁻³

The World Health Organization (WHO) defines nutritional anemia as a hemoglobin level below that which is considered normal for age, sex, physiological state, and altitude, without considering the cause of the deficiency.^{4,5}

Iron deficiency anemia, in its turn, is characterized by the reduction or absence of iron stores, low serum

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concentration of iron, low transferrin saturation, poor hemoglobin concentration and hematocrit reduction.⁶ Initially, the body stores of iron, ferritin and hemosiderin decrease, while hematocrit and hemoglobin levels stay normal. Afterwards, the serum level of iron decreases and, concomitantly, the iron binding capacity increases, which results in a reduction of the percent transferrin saturation. Consequently, there is a swift reduction in red blood cell circulation. This stage is known as *iron deficiency without anemia*. Iron deficiency anemia is the most advanced stage of hypsiderosis, characterized by low hemoglobin and hematocrit, with changes in erythrocyte cytology and morphology, causing microcytosis and hypochromia, in addition to dysfunction of the oxygen transport mechanism.^{7,8}

The reduced hemoglobin concentration, which affects the transport of oxygen to tissues, is characterized by signs and symptoms on the skin and mucous membranes (paleness, glossitis), gastrointestinal disorders (stomatitis, dysphagia), fatigue, weakness, palpitation, reduced cognitive function, growth delay, delayed psychomotor development, in addition to compromised thermoregulation and immunity in children.⁹⁻¹¹ Although homeostatic mechanisms provide a notable adaptation, it is possible to find severe anemia in symptom-free individuals.⁶

Knowingly, the major causes of iron deficiency are depletion of iron stores at birth, decreased iron intake, increased loss of organic iron, reduced iron absorption, and increased iron demand.⁶⁻⁸ There are several factors that contribute to iron deficiency. Just like any other public health problem, iron deficiency anemia originates from a broader context, in which it is not exclusively determined by biological factors, but also by current socioeconomic and cultural aspects.¹²

There is some evidence of a remarkable reduction in the prevalence of malnutrition in the Brazilian population in the last decades.^{13,14} It is still worrying, however, that the behavior of iron deficiency anemia does not seem to follow the improvement of nutritional status, as shown in studies carried out in the city of São Paulo.¹³⁻¹⁶

The present study aimed at reviewing the literature on the determinant factors that could contribute to the health/disease process of anemia. The assessment of each one of these factors and of their interrelationships allows presenting the variables of a theoretical epidemiological model for iron deficiency anemia (Figure 1). This can provide us with subsidies for the formulation of health and nutrition policies that could solve the problem and consequently improve the quality of life of children aged less than five years.

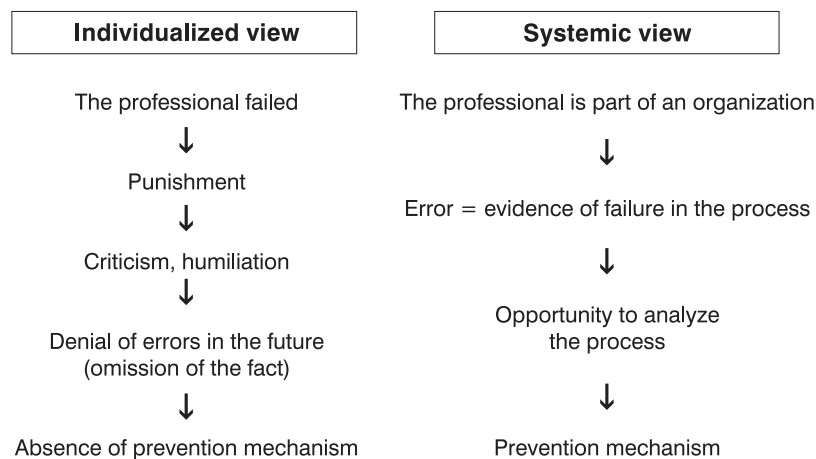


Figure 1 - Hierarchical model of anemia determinant factors

Determinant factors of anemia

Socioeconomic conditions

Even though iron deficiency anemia is not restricted to public health in developing countries, it is important to consider that factors that could aggravate iron deficiency are associated with socioeconomic conditions of underprivileged classes, either due to inadequate nutrition (quantitatively and qualitatively), or due to the lack of sanitation or also other indicators that could contribute directly or indirectly to its increased prevalence.¹² Therefore, the populations that live in rural areas and in the outskirts of urban centers, because of joblessness, low wages, poor housing, education and health conditions, are the ones that are at higher risk for anemia.¹⁷

Population-based studies, in which the prevalence of anemia in urban areas is compared to that observed in rural areas, indicate that iron deficiency anemia is more frequently found in the latter, affecting approximately 50% of the children in Brazilian rural areas.¹⁷⁻¹⁹ The major reasons for the higher prevalence of iron deficiency anemia in rural areas may be associated with low availability of iron-rich foods, especially those high in heme iron and in vitamin C, as well as with the early introduction of foods during the first six months of life, when breastfeeding must be exclusive.¹⁷

Most studies show that the percentage of children with anemia is significantly higher among those from low-income families.²⁰⁻²³ However, this association is not always found.²⁴ In populations that are already considered to have a low income, this association is not observed, since almost the whole population has a similar income.^{24,25} We should not take for granted that an income increase will reduce the prevalence of anemia, since this deficiency is also found in high-income families.²⁶ Sigulem et al.²⁰ have attempted to interpret the interrelationships between the presence of anemia at the ages below and above 24 months and family income. No statistically significance was observed in the cases of anemia among infants aged less than 24 months whose families had an income lower or higher than one minimum wage (approximately US\$ 65). On the other hand, the association between the existence of anemia and the two income levels was significant in infants older than 24 months.

Parents' level of education may be considered an important socioeconomic factor for the occurrence of anemia. A higher level indicates increased chances of having a job and income, and consequently, easier access to iron-rich foods. The mother's level of education, in its turn, influences the practices related to the child's health care. Monteiro and Szarfarc¹⁵ have studied the prevalence of anemia in children aged less than 60 months in relation to the family's socioeconomic level (determined by the family head's level of education) and have shown that, although none of the strata is immune to anemia, the prevalence was

inversely proportional to the level of education. Osório²⁵ has found a linear association between mother's level of education and the increase in hemoglobin concentration of children aged between six and 59 months. However, in the reviewed literature, no association was observed between the presence of anemia and mother's different levels of education.^{20,22,24,27} The explanations to these findings could be the same ones used for the previously mentioned income variable.

Children who have two or more siblings aged less than five years can have a higher risk for anemia. Families with a large number of young children have an increased demand for food and cannot provide their children with appropriate health and nutritional care.²³

Food Intake

Among the factors involved in the causes of iron deficiency anemia, a low-iron diet and the low bioavailability of this mineral are some of the most important.^{15,28}

Iron deficiency during pregnancy, especially in the last three months, increases the number of low-weight preterm newborns. However, the body iron content at birth does not depend on the mother's body iron store, except for the cases of extremely severe iron deficiency. Iron deficiency during pregnancy often causes problems to the mother rather than to the child, since the child uses his/her mother's body iron store to meet his/her requirements. Low iron content at birth, determining the early development of anemia, may be associated with abnormal situations, such as perinatal hemorrhage.^{11,29,30}

Therefore, regardless of factors such as prematurity and low weight, the child has high hemoglobin levels at birth and an iron content equivalent to 75 mg/kg; most of this iron is found in red blood cells (50 mg/kg).²⁹⁻³¹

The iron stored by the fetus is mobilized from the moment of birth, in order to meet the newborn's requirements, imposed by rapid growth and by the restoration of iron lost in the feces and urine and by the skin.³⁰

In the first two months of life there is large reduction in hemoglobin concentration, with lowest values found between the sixth and eighth weeks and a concomitant increase in the mobilization of iron stores. This reduction, known as *physiologic anemia of infancy*, cannot be avoided by any preventive measure and is not accompanied by any disorders.^{30,32}

Iron stores, from birth to the sixth month of life, when the infant receives exclusive breastfeeding, meet the infant's physiological requirements; therefore, they do not have to be supplemented, and solid foods do not have to be introduced.^{33,34} This is due to the high bioavailability of iron in human milk, from which approximately 50% of the iron is absorbed, thus compensating for low iron content (0.5-1 mg of iron/liter). However, this bioavailability can

decrease by 80% when infants are fed other foods. Therefore, the early introduction of complementary foods is a risk factor for the development of iron deficiency anemia.^{35,36} Osório²⁵ has shown that infants who were breastfed for more than four months had a mean hemoglobin level around 3 g/dL higher than those who were not. Torres et al.¹⁸ have found an increase in the prevalence of anemia as the breastfeeding period was reduced, showing a statistically significant association. The influence of breastfeeding over the development of anemia is usually observed in infants aged less than six months; studies with infants aged between 10-14 months³⁷ and 6-62 months³⁸ have shown that breastfeeding is not a predictive factor for iron deficiency.

After the sixth month, iron stores are depleted and nutrition has a crucial role in the supply of this mineral to the infant. Iron intake has to suit the requirements of this age group.^{30,31,39}

From the sixth to the twelfth months, iron requirements increase with body weight, as the infant's weight will have tripled by the end of the first year of life. Approximately 30% of the iron that is necessary for erythropoiesis should come from the food. As the infant shows accelerated growth and depends on food as a source of iron, he/she tends to show a negative iron balance. This situation is totally different in adults, who recycle about 95% of the iron required from the lysis of red blood cells, and need to obtain only 5% of the iron from food.^{29,30}

According to the FAO/WHO committee,³¹ basal requirement is "the amount required to maintain organic functions, compensate for natural iron loss and promote the infant's body development, thus restoring and maintaining iron stores as a guarantee against a future increase in the requirements or reduction of iron intake". FAO/WHO considers that iron requirements can be determined according to the individual's basal requirement. The requirements are initially considered according to the amount of absorbed iron. These requirements are then converted in order to estimate the iron requirements in the diet, taking its bioavailability into consideration. The requirements of absorbed iron are 0.96 mg for infants between three months and one year of life; 0.61 mg, between one and two years; and 0.70 mg, from two to six years.³¹ Thus, depending on the quality of the diet, an intake of 10 to 20 mg of iron/day is necessary to meet the requirement of 1 mg of absorbable iron of infants and children.³⁰

Until some time ago, iron intake within the limits or above the recommended values was believed to satisfactorily prevent iron deficiency anemia. As a result, several studies have failed to associate total iron intake with organic iron.⁴⁰⁻⁴² However, studies of the bioavailability of nutrients have shown that it is more important to pay special attention to the amount of bioavailable iron than to meet iron requirements, because bioavailable iron is correlated with stimulating and inhibitory factors found in the same meal.^{43,44}

Iron is found in foods in heme and non-heme forms. Heme iron, encountered in meats and entrails, has a high bioavailability and is not exposed to inhibitory factors. Meats have approximately 4mg of iron per 100g, with an absorption of approximately 40%.^{5,31,45,46}

Non-heme iron, found in cereals and vegetables, contrary to animal iron, has an absorption of only 10%. The absorption of non-heme iron is strongly influenced by various dietary components.^{5,31,45,46}

A low-meat diet is often more common in low-income families, causing a poor use of biological iron. Apparently, economically underprivileged individuals consume fewer iron-rich foods and also have a low intake of bioavailable iron, due to their trivial diets, which include cereals, and low amounts of meat and foods rich in vitamin C.⁴⁷

By assessing the diet of children in terms of quality and quantity of iron intake, one can observe that iron of vegetable origin is consumed more often than that of animal origin, and that there is an increased rate of inadequate intake of total iron among children aged less than 24 months.^{20,25}

When the mean energy and iron intakes are analyzed, one observes that dietary iron deficiency does not stem from calorie deficiency, but rather from an iron-specific dietary inadequacy.^{48,49} Szarfarc et al.⁴⁹ have discovered that iron deficiency in the second year of life would not exceed energy deficiency, and that before this age it would, thus suggesting that the main cause of this problem at this age is concerned with dietary composition. Monteiro et al.¹⁶ have analyzed the variations of indicators of energy and iron intake over time among the epidemiological surveys carried out from 1984/85 to 1995/96, and have found an increase in energy and iron intake. However, the energy density of iron was not modified during this period, which justifies the high prevalence of anemia in both surveys, but does not explain its increase during this period, which probably occurred due to some changes in children's eating patterns.

The wide variety of factors that stimulate and inhibit iron absorption is well-known.^{45,46} Two powerful stimulators of non-heme iron absorption are meats and vitamin C. Several animal tissues, including beef, poultry, fish, goat, liver and pork, increase iron content once they provide a high availability of heme iron and enhance the absorption of non-heme iron. When ascorbic acid is added to the diet, there is a remarkable increase in iron absorption.^{50,51}

Phytates, tannins (polyphenols), calcium, phosphates, eggs, and other types of food inhibit iron absorption by forming precipitates that bind to iron, thus hindering its absorption.^{50,52,53} Fibers alone have no influence over iron absorption. The inhibitory effect of whole cereals is also attributed to phytate content.⁵⁴ The inhibitory effect of calcium on iron absorption has a considerable nutritional importance. Studies of nutritive components of food have

shown that milk-derived calcium strongly inhibits the absorption of heme and non-heme iron. However, a mechanism that produces a direct effect of calcium on iron absorption is still unknown. There may probably be some competitive inhibition between calcium and iron in the final transport from the intestinal mucosa to the plasma, which is valid for both heme and non-heme iron.^{53,55,56} The inhibitory effect of cow's milk on iron absorption may also be due to the presence of phosphoproteins. In eggs, phosphoproteins found both in yolk and white have an inhibitory effect.⁵⁴

Although the absorption of dietary iron is reliant on several factors, such as type of iron consumed, organic reserves of iron, and combination of foods in the same meal, it is possible to predict the absorption potential in each of the daily meals, by means of the equation created by Monsen and Balintfy.⁴⁴ This equation takes into consideration iron content and the factors that strengthen iron absorption (meats and vitamin C) found in the composition of each meal. The sum of the values observed in different daily meals corresponds to the daily amount of bioavailable iron under normal physiological conditions.

By using the equation created by Monsen and Balintfy, Osório²⁵ has found low bioavailability of iron in children aged between six and 59 months, in all age groups and geographical areas of the state of Pernambuco, Brazil.

It is therefore evident that an adequate energy intake is no guarantee for an adequate iron intake.^{48,49} One should also consider that the quantification of iron intake poorly elucidates its adequacy. Iron absorption is qualitatively related to the total dietary intake, since specific foods are required for the improved use of iron by the body. Thus, the assessment of specific diet factors concerned with iron absorption is extremely important so that the epidemiology of iron deficiency anemia can be clearly understood.

Health care

Prenatal and delivery care should be efficient in avoiding and correcting the main problems associated with the health and nutrition of pregnant women, which could be the cause of low birthweight and prematurity (risk factors for anemia). Similarly, in puerperium, the follow-up of child growth and development, which must include appropriate information about breastfeeding and supplementary foods, can substantially reduce the risk for anemia.

In Australia and in the United States, for instance, iron deficiency is no longer a public health problem in school-age children. Possibly, the reduction of iron deficiency rates in the last few years has been due to the improvement of child health care, increased rate of breastfeeding, improvement of nutritional status, and to the implementation of healthy eating habits. In addition, the policy of food fortification adopted by these countries is quite relevant.^{28,38}

The lack of appropriate health care that could prevent anemia and early identify children with iron deficiency does not allow the timely treatment of such condition. For this to happen, health services should implement nutritional assistance to children and pregnant women on a regular basis by assessing their nutritional status and offering them nutritional education. It is also important that these services perform a laboratory diagnosis of anemia and offer patients drug treatment against this disease. The government should also implement programs for food supplementation and/or fortification with iron as measures to control and combat anemia.

Nutritional status

Anemia of pregnancy, especially in the third month, increases the risk of birth of preterm and low-weight babies. Low birthweight, an indicator of malnutrition at birth, is regarded as a determinant factor for anemia, especially in children aged less than one year.^{25,27,37} Even if preterm or low-weight newborns have, on average, the same iron content per kilo as full-term newborns, the total iron store is lower, while their postnatal rate of growth is higher.¹¹ Therefore, the depletion of iron stores occurs earlier, rendering these newborns dependent on exogenous sources of iron and opening the way for the development of anemia.^{11,34,57} On the other hand, Monteiro and Szarfarc¹⁵ consider that low birthweight does not fully explain the early development of anemia in the city of São Paulo, since the incidence of low birthweight in the population is low. The same train of thought could be followed for the state of Pernambuco where, in spite of no correlation between hemoglobin concentration and birthweight, the latter variable does not explain the high prevalence of anemia, especially in the rural area, where a lower incidence of low birthweight and a higher prevalence of anemia among children in this state were observed.^{14,25}

Malnourished children are often anemic.^{17,21,57} Protein deficiency in protein-energy malnutrition reduces hemoglobin concentration by 20%, which seems to be an adaptation of the organism to the reduction of muscle tissue.⁵⁸ Nevertheless, although there is some evidence of a considerable reduction of malnutrition among Brazilian children, the epidemiology of iron deficiency anemia has not shown the same trend.^{13,15,16}

Studies have shown that there is a relationship between serum retinol and hemoglobin concentration, which indicates that vitamin A deficiency and anemia usually coexist. These studies also state that anemia could be a consequence of vitamin A deficiency.^{51,59,60}

It has been suggested that vitamin A influences iron metabolism; however, this mechanism has not been fully explained yet. It is unlikely that vitamin A could interfere directly with intestinal absorption of iron; it could however

mobilize available iron stores and use the iron to form hemoglobin.^{51,60-62} Another possibility is the reduction of transferrin level by vitamin A deficiency, which then reduces iron transportation.⁶²

In areas where vitamin A deficiency is endemic, programs for food supplementation or fortification with vitamin A can increase the concentration of organic iron in the population.^{60,63-65}

Morbidity

The literature on the association between iron deficiency and infections is controversial. Some authors say that any iron deficiency suppresses the immune system and increases the risks for infection, while other authors affirm that the immune system profits from a slight iron deficiency. The changes in iron metabolism induced by inflammation and infections are important confounding factors when iron content is assessed.^{66,67}

It is well-known that gastrointestinal and respiratory infections often predispose to the reduction of serum iron levels in the body due to the reduced production of hemoglobin and decreased iron absorption.⁶⁸⁻⁷⁰

Iron deficiency, in its turn, suppresses the immune system and, consequently, some pathogenic agents can have a higher virulence in iron-depleted environments and enhance the risk of infection.^{70,71}

The idea that iron deficiency can be a protective factor against infections is based upon studies that have shown that iron is necessary for the growth and/or production of bacterial toxins. Some authors have proposed that, instead of considering anemia in infections and chronic diseases as a disorder associated with infection/inflammation, such anemia could be a nonspecific immunological defense mechanism, considered as host response to microbiological invasion. Therefore, this anemia could be reversible, and would not be associated with iron deficiency in most cases.⁷²⁻⁷⁴ Olivares et al.⁷⁵ have observed that mild viral infection, which occurs after the administration of the antimeasles vaccine, substantially reduces hemoglobin concentration as well.

No studies that associate iron deficiency with diarrheal diseases have been found. There are vast possibilities of anemia after an acute infection episode, and these possibilities vary according to the length and severity of the disease.⁷² Reeves et al.⁶⁸ have shown that mild diarrheal diseases affect approximately 60% of children aged less than one year, between the ninth and twelfth months of life, and that these diseases are associated with low hemoglobin concentration.

Since there is some evidence that anemia is commonly found among children with mild infections, especially among those aged less than one year, and that these infections leave

a residual effect on healthy children, it has been suggested that the tests for the diagnosis of anemia be performed two or three weeks after the end of infection.⁶⁹ This procedure should also be carried out after immunization, as recent vaccination could considerably reduce hemoglobin concentration.⁷⁵

Several authors say that intestinal parasitic diseases are some of the factors related to the loss of organic iron.^{8,76,77} However, recent studies seem to suggest that parasitic diseases have a secondary importance in the etiology of iron deficiency anemia in children aged less than five years, since these diseases usually occur in older children who, according to the data, seem to be less prone to anemia.^{15,78}

Biological factors

The child's age is another risk factor for anemia. All studies in which children are assessed according to age show a higher prevalence of anemia in children aged between six and 24 months.^{15,23,24,38,79} Osório et al.¹⁷ have demonstrated that children between six and 24 months have a significantly higher prevalence of anemia (twofold) when compared to children between 24 and 59 months.

Surprising data have been reported in 512 northeastern Brazilian towns with a high level of malnutrition: 82.7% of children aged between 11 and 13 months were anemic.⁸⁰

From the 24th month on, the prevalence of anemia tends to decrease linearly.^{15,21,24,25}

In the two first years of life, growth and development accelerate in children and they need a higher amount of iron.^{30,31} Even though iron requirements decrease with age, the consumption of different foods, as a result of growth and development, allows obtaining an adequate iron content quite easily. In younger children, a trivial diet, poor in iron and vitamin C, does not allow easily reaching the cutoff point for anemia established for children aged less than five years.^{17,30,31}

Most authors have shown that there is no difference in the prevalence of anemia or hemoglobin concentration in terms of sex.^{17,27,81,82} On the other hand, Torres et al.¹⁸ have demonstrated that the prevalence of anemia can vary between males and females; they have justified their findings by stating that "the higher prevalence of anemia among boys has to do with their higher growth rate; during the growth stage, their bodies demand a higher amount of iron, which cannot be supplied by the diet".

Final considerations

At the end of the 1990s, the commitment taken on at the New York Summit Meeting⁸³ was not fulfilled. Despite the aim of reducing the prevalence of anemia in children and

pregnant women by one third, the problem appears to deteriorate in these risk groups.

Given the scope of the problem and the involved risk factors described in our article, we suggest the implementation of urgent measures for the prevention and treatment of iron deficiency anemia. We underscore that the multiple causes of anemia determine the multiple strategies that can be effective in combating the problem. A single strategy might not be so successful if other measures are not taken simultaneously.⁸³

Health and nutrition programs are more urgently needed in the age group at higher risk (six to 23 months). It is also important to give some special attention to rural and risk areas, in which low socioeconomic conditions aggravate the status of anemia, as iron-rich foods cannot be easily obtained.

Short-term measures, such as administration of ferrous sulfate, have proved feasible. Recent studies have shown that the intermittent or weekly treatment seems to be efficient, reducing side effects and the costs of intervention of broad coverage programs.⁸⁴⁻⁸⁸

Iron-fortified foods (wheat flour, corn flour, and milk), which are predominantly used in a child's diet, can be consumed in the short run. Milk fortification has proved efficient in the reduction of the prevalence of anemia and iron deficiency.⁸⁹⁻⁹¹ The fortification of other kinds of food could be problematic, especially in subsistence farming areas. The fortification of foods such as sugar and salt, which are usually consumed by the economically underprivileged population, is difficult because many producers are involved and, therefore, a standardized process would be hard to implement. Another possibility would be to fortify drinkable water, which has been considered to be a good carrier of iron and a good way to reduce the prevalence of anemia among preschoolers.⁹²

Even in the medium or long run, nutritional education activities have a potential effect in terms of cost-benefit.⁹³ Nutritional advice should be provided together with any other measure with the aim of changing eating habits with regard to the selection, combination and preparation of foods. The consumption of different kinds of food, especially those rich in iron, should be stimulated by the indication of lower-cost sources of iron, such as entrails. The consumption of foods rich in vitamin C and iron in the same meal should be encouraged, since this favors the absorption of non-heme iron.²⁸

A high-impact preventive measure is the encouragement of exclusive breastfeeding up to the sixth month of life and the implementation of supplementary foods after this age.

The control and treatment of infectious and parasitic diseases should be implemented in health and sanitation areas, with the aim of reducing the risk of low hemoglobin concentration.

Further studies are necessary to assess iron intake and the bioavailability of iron for children, since there exists no specific methodology for such assessment. Systematic surveys on iron intake have to be carried out. Mineral content of foods may vary because of non-nutritive sources, such as water, soil, and climate, and because of the utensils used in their grinding and cooking. In addition, there is no information about the nutritional components of several currently consumed foods and about the nutritional content of prepared dishes.⁹⁴ Therefore, it is necessary to elaborate new food tables and programs for dietary calculation, which show the nutritional components of foods, regionally consumed preparations, and of portions or measures often used by local populations.

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