Considerations on the food fortification policy in Brazil

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Government health authorities approved, in December 2002, the ANVISA (National Sanitary Vigilance Agency) resolution number 344, making the addition of iron and folic acid to all wheat and maize flours industrialized in Brazil obligatory. After a brief review of iron deficiency, iron overload and folic acid deficiency several questions and remarks need to be made about this universal food fortification program. Iron salts and folic acid are drugs widely used in medicine and they may present undesirable side effects. There are potential risks with offering iron to the normal population for a long period of time and to patients with iron overload. Other important remarks are: there is no medical follow up of this treatment in the Brazilian population; patients can decide the quantity of foods (and of these nutrients) that they want to ingest; fortified foods may correct iron deficiency anemia but not necessarily the causes, which include gastrointestinal neoplasms; and folic acid in the diet may interfere with several treatment protocols that use folic acid antagonists, such as methotrexate. Finally, with the exception of some social programs, the costs of treatment using fortified foods are passed on to the population. Considering that Brazil has 330,000 active medical doctors it is suggested that our Health Ministry should invite them to take care of these important medical conditions.

Keywords: *Anemia, iron-deficiency; Iron overload; Folic acid deficiency; Food, fortified*

Introduction

Iron is part of the hemoglobin molecule whose function is to transport oxygen from the lungs to tissues. In the body there are other molecules that contain iron, such as myoglobin and certain enzymes, which also play vital functions.

The estimated total amount of iron in the body is about 4 g; 2.5 g in hemoglobin, 0.5 g in myoglobin and enzymes and 1.0 g as a reserve.

The blood undergoes a continuous process of renewal. Usually 20 mL of red blood cells are produced per day to replace the same amount that is destroyed. The iron from normal cell destruction is reused to form new blood.

The daily requirement of iron in humans is 0.9 mg, which is enough to replenish the amount lost by the desquamation of skin, intestinal and urinary tract cells. This is the only physiological mechanism to excrete iron from the body.[1]

For women of childbearing age, iron requirements increase to 1.3 mg per day due to menstrual blood loss and in pregnant women, requirements increase to 3.0 mg per day. During child growth this need also remains high.

Replacement iron is attained from food. The amount of iron in food varies with the highest quantities being absorbed from meat, in particular liver, eggs and nuts. The absorption capacity of this metal in the intestine decreases when it is bound to phytates (in beans) or phosphates (as in egg yolk). These foods do not have good bioavailability of iron. On the other hand, iron bound to heme (as in red meat) is very well absorbed, as is iron in some salts such as ferrous sulfate.

A normal diet contains 14 mg of iron, an amount far in excess of daily requirements.

Iron deficiency in the organism

Iron deficiency is the most frequent hematological abnormality; it affects 20%-30% of the world population, especially children, women of childbearing age and pregnant women.[2,3] Its prevalence varies according to the region and socio-economic conditions.

Despite of the great evolution of medicine over recent years, there is still a high prevalence of iron deficiency anemia in Brazil. Szarfarc,[4] discussing the high prevalence of this condition in the infant population, presented the results of studies (56% of children

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attending state services have anemia in the first year of life). Additionally, other Brazilian researchers such as Fisberg et al.[5] found an incidence of anemia in 75% of Brazilian children in daycare centers and Torres et al.[6] identified anemia in 59.1% of 6 to 23-month-old children attended in government healthcare clinics in the state of São Paulo.

The Food and Nutrition Policy General Committee of the Ministry of Health addressed the epidemiological relevance of this issue and reported that, despite of not having complete national figures, studies show that approximately half of Brazilian preschool children are anemic (about 4.8 million children), with the prevalence reaching 67.6% in 6 to 24-month olds. In regards to pregnant women, the estimated national average of anemia is approximately 30% (http://nutricao.saude.gov.br/ferro.php).

The most common causes of anemia are blood loss due to chronic injuries of the digestive tract (duodenal ulcer, stomach cancer, cecum cancer, diaphragmatic hernia, hemorrhoids, etc.) gastrectomy, hypermenorrhea, frequent pregnancies, intestinal infestations by Necator or Ancilostoma, taking acetylsalicylic acid (aspirin) and anti-inflammatory medications, growth, malnutrition, hereditary telangiectasia and repetitive bleedings.

The disease is expressed clinically as pallor of the skin and mucous membranes, weakness, dizziness, headache, perversion of appetite (parorexia), dysphagia, papillary atrophy, circulatory disorders, koilonychia, late physical growth and delayed mental development with changes in cognitive function affecting learning and school development.

Treatment of iron deficiency anemia is by the oral or parenteral replacement of iron,[7,8] and when necessary blood transfusions. Supplementation should preferably be initiated orally and should be continued until the normalization of iron reserves. It is of utmost importance that the physician determines the cause of the disease that leads to this deficiency. The impact of nutritional counseling and food fortification with iron has been discussed extensively in recent studies.[9-11]

Diseases related to iron overload

Hereditary hemochromatosis[12,13] – the prototype of these diseases – is an autosomal recessive disease due to an abnormality of the HFE gene in chromosome 6, with C282Y being the most frequent mutation. This is highly prevalent in countries of northern Europe and has also been observed in the Brazilian Caucasian population.[14,15] There are other chromosomal abnormalities found in Brazil such as the H63D, S65C and V256I mutations. The disease has aroused interest among Brazilian hematologists with the presentation of statistics at national conferences.[16-19] In this disease there is an inappropriate increase of iron absorption by the intestine with the surplus of the metal accumulating in tissues. This disease evolves with liver cirrhosis (30% complicated with liver cancer), splenomegaly, severe heart disease, insulin-dependent diabetes, endocrine disorders and neuropathy.[20-22] The deposit of iron and melanin in the skin gives patients a dark color, hence the term "diabetes tan". Treatment is focused on removing excess metal by repeated bloodletting and the use of oral chelators.

Iron overload can also be found in thalassemia major, sideroblastic anemia, sickle cell anemia, in multiply transfused patients and in individuals who take excessive amounts of medicinal iron.[12,13] In some contingencies iron overload can be extremely high.[23-25]

In the state of Ceará, there are no studies on the incidence of diseases related to iron overload. We tried to approach this problem from three aspects: studying serum ferritin in patients in a clinical pathology laboratory of the city, examining the findings of magnetic resonance imaging to assess iron deposits in diseased liver at a specialized service and evaluating the number of multiply transfused patients in a state hospital in Fortaleza.

Petrola, Z, in the Emilio Ribas Laboratory, analyzed a total of 2331 results of serum ferritin examinations in July and August 2009 and January 2010 (Personal communication). Of these, 302 (12.95%) presented figures above 365 ng/mL. Sixteen sick patients had more than 2274 ng/mL with the highest value being 30,400 ng/mL.

A service of magnetic resonance using T2*-weighted sequences was recently installed in the city by Carlos, E. (Personal communication) who reported that among 64 patients studied, five had low concentrations of iron in the liver and 59 (92.18%) had moderate to high loads.

Finally a study on the number of multiply transfused patients was carried out by Charles L. (Personal communication) in the Hospital Geral de Fortaleza, a state hospital with 413 beds, 84 of which are for emergency. In 2009, this unit performed a total of 13,180 blood component transfusions, of which 8,155 were packed red blood cells. Eighty patients were transfused more than 10 units of packed red blood cells, with one patient receiving 51 units.

This approach has no statistical value but shows the existence of large numbers of people with iron overload in this region. It just goes to demonstrate that planned national scientific studies are urgently needed to determine the prevalence of iron overload diseases in Brazil.

General information on folic acid

Folic acid is the common name for pteroylmonoglutamic acid. Its deficiency produces a macrocytic (megaloblastic) anemia where red blood cells are large due to a decrease in DNA synthesis.[26,27]

Folic acid is synthesized by plants and bacteria with the main sources for humans being fresh fruits and vegetables. The minimum daily requirement of vitamin A is 50 mcg; the greatest part of the reserve, which varies from 50 to 20 mg, is in the liver. This reserve is not large as it may

become depleted within a few months of reduced intestinal absorption or insufficient intake.[26]

Importantly, some forms of folate are labile and can be destroyed by cooking. Therefore, adequate amounts of this vitamin in the diet depend on the diet and manner of food preparation.[28-30]

Causes of folic acid deficiency include:

– Inadequate intake: alcoholism, drug use associated with poor nutrition;

– Increased need for folic acid: in hemolytic anemias, other active erythropoiesis, folic acid deficiency in the first weeks of pregnancy leading to defects in neural tube formation and myelomeningocele,[28] periods of rapid growth of children and adolescents and hemodialysis;

– Malabsorption: tropical sprue, non-tropical sprue and primary disorders of the small intestine;

– Use of anti-folic acid drugs: methotrexate, trimethoprim, pyrimethamine and triamterene.

Studies on food fortification

The problem of food fortification as a strategy to prevent the high incidence of iron deficiency anemia has been the subject of investigations by many Brazilian and foreign researchers. We will address some of them.

In 2007, Assumption & Saints[31] made an important analysis of the results of 21 studies conducted in Brazil and abroad about the effect of food fortification with iron on anemia in children. They concluded that there is no convincing proof of efficacy or effectiveness of food fortification with iron on the prevalence of anemia in children in the studies analyzed.

Recently Szarfarc,[4] discussing public policies to control anemia in Brazil, reviewed several studies on the fortification of foods with this nutrient, and reported some good results and others that did not demonstrate the expected effectiveness. As for the current government's policy of food fortification with iron and folic acid, there seems to be few and contradictory outcomes and the occurrence of anemia among pregnant women may remain unchanged one year after implantation.

Vellozo & Fisberg[10,11] also reviewed the issue and after evaluating several studies from Brazil and abroad they highlighted the need to seek new more efficient and appropriate ways to fortify food. They believe that the issue still needs to be discussed in academic, governmental and institutional settings.

Prevention of neural tube defects using folic acid

In 1991 the MRC Vitamin Study Research Group published a major work on the prevention of neural tube defects with folic acid.[28] This is a cooperative group formed by 33 medical centers in seven nations (Britain, Hungary, Israel, Australia, Canada, Russia and France) which demonstrated that the intake of folic acid prevented the appearance of neural duct defects in pregnant women who had had similar cases previously. Jacques et al.[30] approached the problem differently showing that the fortification of cereals with folic acid was associated with a substantial improvement in folate concentrations in the blood in elderly and middle-aged populations residing in New England, USA.

Questions and considerations of the food fortification policy adopted in Brazil

On 13 December 2002, the Brazilian government adopted resolution # 344 of the Brazilian National Health Surveillance Agency (ANVISA) making it mandatory to add at least 4.2 mg of iron and 150 mcg of folic acid per 100 g of wheat and maize flour produced in Brazil. Companies had a period of 18 months to comply.[32]

The concern of the Ministry of Health to adopt strategies to reduce the high incidence of anemia and neural tube defects in Brazil is commendable. However, medical literature shows that not all scholars are enthusiastic about food fortification with iron. Adamson,[33] on discussing this problem, reported that it is noteworthy that there has been a decrease in interest in the supplementation of this metal in bread and cereals because of the prevalence of the hemochromatosis gene which leads to a high risk of iron overload.

Iron and folic acid are medications used in medical practice and as such have both beneficial and adverse, or even harmful implications to health. The beneficial effects have been widely examined in studies on the subject, but little has been discussed about the toxicity of these drugs in the healthy population and in patients with diseases involving iron overload.

Remembering that flour is staple in our diet, we can conclude that every citizen residing in Brazil, due to their normal nutritional needs, regardless of age, gender, racial background, occupation, socioeconomic status, healthy or carrier of a disease, will eat iron and folic acid every day, whether they require it or not.

In order to contribute so that a better assessment is made of the Food Fortification Policy implanted in Brazil in 2002, we will discuss this question further.

Adverse effects of iron from fortified foods

The obligation to fortify foods with iron does not worsen the health of normal people but what about patients suffering from illnesses related to iron overload? This is the crux of the question!

The chronic use of medicinal iron is considered a cause of diseases related to iron overload.[12,13] Table 1 shows a simulation of an adult's diet. In this case 34 mg of iron are ingested daily, in part, due to an enriched diet. It is possible

Table 1 - Total amount of iron in a daily fortified diet of an adult (simulation)

	Iron (mg)	Total iron (mg)
Amount of iron in the normal diet		14.0
Iron in fortified foods		
Small bread (50 g each) at breakfast, lunch and dinner	6.0	
Cereal - one portion	3.0	
Total milk or fortified soy milk - 200 mL	2.2	
Pasta - 100 g wheat flour	4.2	
Cake for breakfast, lunch and dinner - 100 g of wheat flour	4.2	
Biscuits, cookies, crackers, etc...	0.4	
Total amount of iron in fortified foods		20.0
Total iron in enriched diet		34.0

to question whether such a diet over a long period of time could cause adverse effects.

Despite of not having a national survey on the prevalence of iron overload diseases, this does not seem to be a good enough reason to compel these patients to run the risk of enriched diets.

Currently, patients with iron overload have no other choice but to ingest this metal even with the potential risk of aggravating their disease. The same is not true for diabetic patients and those who cannot eat gluten; they find products on the market that they can eat!

Need for monitoring of the population that ingests iron and folic acid

This is another important issue! Taking into consideration that iron salts and folic acid are pharmaceutical drugs, it is essential to routinely monitor the population that eats these potentially toxic drugs. This measure is practically impossible in Brazil because of its huge population and large territory. Moreover Resolution #344 of ANVISA is unknown to many Brazilians.

The lack of guidance allows citizens to decide the amount of fortified foods that they should eat and, indirectly, the amount of iron and folic acid. Are we permitting self-medication?

It was an important decision taken by the Ministry of Health to introduce law #1793 of 11 August 2009 creating an interagency commission for the implementation and monitoring of stocks of fortified wheat and maize flour and the byproducts.[34]

What are the maximum amounts of iron and folic acid that can be added to wheat and maize flour?

ANVISA Resolution #344 only stipulated the minimum amounts of iron and folic acid that should be added in the wheat and maize flour enrichment program. There is no limitation on the maximum quantity. Thus, the producer is theoretically free to increase the quantities of these drugs in their products.

It is important to remember that high doses of iron can produce acute, even fatal, poisoning in children. As for folic acid, the MRC Vitamin Research Study Group concluded that it is quickly excreted and toxic effects are unknown.[28]

Medicinal interactions

The intestinal absorption of iron salts may be altered when individuals take antacids or tetracycline and simultaneously drink milk, coffee or tea or eat eggs or dairy products. On the other hand vitamin C – frequently self-medicated in Brazil – greatly increases the absorption of iron.

These observations show how unpredictable the results of a diet enriched with iron salts to solve a major national problem can be. This perhaps justifies the numerous studies reporting that food fortification does not give the expected effects.[4,11,31]

The specific case of iron deficiency anemia in cases of digestive tract cancer

It is not recommended to treat patients without knowing the cause. A patient with digestive tract cancer, particularly at the start of the cecum, often goes to a doctor because of chronic blood loss anemia. The diagnosis of the disease that caused the anemia should be made with some urgency before the tumor becomes inoperable. Thus, an iron rich diet may correct the anemia, but would delay the diagnosis of the cause, which is likely to be made only when the tumor is at an advanced stage.

The specific case of pernicious anemia and folic acid intake

A patient with macrocytic (megaloblastic) anemia should never be treated empirically with folic acid before the determination of the cause of macrocytosis, as neurological lesions may be aggravated if the patient has pernicious anemia.

There is also a potential danger of a diet fortified with folic acid triggering irreversible neurological damage in patients with vitamin B12 deficiency but without anemia.[35]

Folic acid antagonist: Methotrexate

Methotrexate (a-methopterin) is a drug that was introduced into the medical practice in the late forties for the treatment of malignant diseases.[36] It is a folic acid antagonist used in treatment protocols of children with acute lymphoblastic leukemia; this regimen may, according to some authors, provide cure rates of 80%. This drug is also used to treat other cancers such as high-grade lymphomas, choriocarcinoma and some bone tumors.

Methotrexate is widely used in the treatment of rheumatic diseases such as rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, polymyositis and arteritis.[37]

Will folic acid in fortified diets interfere in the success of treatment regimens?

The amount of folic acid and iron in pre-prepared foods

The content of nutrients in enriched flour has been monitored routinely by the government in Brazilian flourmills. In Campinas, SP, Soeiro et al.[38] showed that the wheat flour in shops had higher than expected iron content and low folic acid content. We believe that for a better evaluation of this program, it is of fundamental importance to determine the amount of these elements in pre-prepared products.

In the basic work on the prevention of neural tube defects by the MRC Vitamin Research Study Group[28] one observes the great concern of the authors with the precise dosage of folic acid. Capsules, prepared in Britain, of 4 mg were used and checked every 3 months in a laboratory in Switzerland.

Folates are labile, i.e. easily destroyed by heat.[26,28,29] It is therefore of vital importance to verify that the folic acid added to flour withstands the high temperatures of the baking and industrialization processes of products such as breads, cakes, cookies, etc..

It is well known that ferrous sulfate has good stability with negligible effects during cooking and processing.[39]

Costs of treatment and prevention of iron deficiency anemia with universal food fortification

Beutler et al.[40] call the attention that treatment of patients with iron deficiency anemia with an iron salt (such as ferrous sulfate) is efficient and cheap. With the exception of gastrointestinal disorders and other less severe diseases, the treatment of iron deficiency is effective in most cases with hemoglobin levels and iron reserves being quickly corrected.

Analyzing the problem solely from the perspective of costs of treating iron deficiency two points deserve mentioning:

– One ferrous sulfate tablet sold in pharmacies is relatively inexpensive and contains 40 mg of iron. On the other hand, with the current food fortification program, a kilogram of bread or cake contains an equal amount of iron at a very much higher cost;

– On analyzing this policy, it can be concluded that, except for some social programs, the cost of treatment of anemia in Brazil is passed on to the consumer!

This policy may eventually result in failure of this method of treatment for lack of adherence of the low-income population. This hypothesis was raised by Szarfarc[4] in a recent study.

Final considerations

The strategy of universal food fortification does not seem to be the ideal method to solve the problem of the high prevalence of iron deficiency anemia in Brazil. Besides the observation that many studies showed that the efficacy and effectiveness of iron fortification, both universal and targeted diets, have not yielded the expected results[4,31] there is the danger of toxicity in healthy populations and in patients with iron overload diseases.

Universal food fortification may be a saving measure in developing countries or in those with serious economic and social problems such as a lack of doctors, poverty, hunger, disease, civil war, etc.. However, apparently all these factors do not apply to Brazil. In relation to the number of physicians, according to the Federal Medical Council,[41] Brazil had 330,000 active physicians in 2008, i.e., approximately one to 545 inhabitants. Apart from this very high number of physicians relative to the population, we also have state healthcare in most Brazilian cities and specialists in hematology, nutrition, pediatrics, obstetrics, internal medicine and family health medicine. We believe that with coordinated by the Ministry of Health, these professionals can solve the serious problem of iron deficiency anemia in Brazil!

Finally, our flour producers that cooperated so much with the wheat and maize flour fortification policy implanted in Brazil in 2002, would not suffer large losses with possible future legal cases, since they will be able diversify their industrial products, with or without enrichment with nutrients.

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