Nutrición Hospitalaria

Nutr Hosp. 2014;29(6):1240-1249
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Iron deficiency anemia in adolescents; a literature review

Romilda Castro de Andrade Cairo, MD, MSc[1], Luciana Rodrigues Silva, MD, MSc, PhD[2], Nadya Carneiro Bustani, MSc[3] and Cibele Dantas Ferreira Marques, MSc[4]

[1]Doctoral student in Medicine and Health, School of Medicine, Federal University of Bahia. Preceptor of the Department of Pediatric Gastroenterology and Hepatology, Professor Edgard Santos Teaching Hospital. Pediatrician, Emergency Department, Hospital Aliança. Member of the Bahia Society of Pediatrics (SOBAPE). Salvador, Bahia, Brazil. [2]Head of the Department of Pediatrics, Head of the Department of Pediatric Gastroenterology and Hepatology, Professor Edgard Santos Teaching Hospital. Permanent member of the Postgraduate Program in Medicine and Health, School of Medicine, Federal University of Bahia. Salvador, Bahia, Brazil. [3]Adjunct Professor of Pediatrics, School of Medicine, Federal University of Bahia (retired). Salvador, Bahia, Brazil. [4]Assistant Professor, School of Medicine, Federal University of Bahia. Preceptor of the Department of Pediatric Gastroenterology and Hepatology, Professor Edgard Santos Teaching Hospital. Pediatric Gastroenterologist and Hepatologist, Hospital Central Roberto Santos. Salvador, Bahia, Brazil.

Abstract

Introduction: **Anemia is one of the most important nutritional deficiencies affecting various social and socioeconomic strata. It is more common in developing countries, with children and adolescents being at a significantly higher risk for the condition.**

Objective: **To perform a literature review on iron deficiency anemia in adolescence as a public health issue and on the risk factors that may contribute towards nutritional deficiencies, stunted growth and development in this age group, emphasizing the physiopathology and causes of anemia, the different diagnostic approaches, and its clinical characteristics, prevention and treatment.**

Methodology: **The LILACS-BIREME, SCIELO and PUBMED databases were consulted for the study. Scientific papers published in Spanish, Portuguese or English between 2000 and 2013 on the subject of iron deficiency anemia in adolescents were selected for inclusion. A total of 102 studies published between January 1st, 2000 and June 30th, 2013 were identified and evaluated. Forty-two articles meeting the inclusion criterion (adolescents with anemia) were selected for this review. Finally, an analysis was conducted and the papers were evaluated in accordance with the study objectives.**

Results and Discussion: **The studies reviewed revealed a prevalence of iron deficiency anemia of around 20% in adolescents and described the harmful effects of anemia in this age group.**

Conclusion: **Preventive action is required with respect to iron deficiency anemia. Healthcare professionals should be aware of the need for early diagnosis, prophylaxis and treatment.**

(*Nutr Hosp.* 2014;29:1240-1249)

DOI:10.3305/nh.2014.29.6.7245

Key words: *Iron deficiency anemia. Iron deficiency. Adolescent.*

Correspondence: Romilda Castro de Andrade Cairo.
Alameda dos Antúrios, 178. Apdo. 702.
Cidade Jardim, Candeal.
40.296-530 Salvador. Bahia. Brazil.
E-mail: romildacairo@terra.com.br

Recibido: 19-XII-2013.
1.ª Revisión: 5-III-2014.
Aceptado: 12-III-2014.

ANEMIA POR DEFICIENCIA DE HIERRO EN ADOLESCENTES; UNA REVISION DE LA LITERATURA

Resumen

Introducción: **La anemia es una de las deficiencias nutricionales más importantes que afecta a varios estratos sociales y socioeconómicos. Es más frecuente en países en vías de desarrollo, estando los niños y los adolescentes en un riesgo significativamente mayor para padecer esta afección.**

Objetivo: **Realizar una revisión bibliográfica sobre la anemia ferropénica en la adolescencia como un problema de salud pública y sobre los factores de riesgo que podrían contribuir en las deficiencias nutricionales, la detención del crecimiento y el desarrollo en este grupo de edad y poniendo el énfasis sobre la fisiopatología y las causas de la anemia, los diferentes abordajes diagnósticos y sus características clínicas, la prevención y el tratamiento.**

Metodología: **Para este estudio, se consultaron las bases de datos LILACS-BIREME, SCIELO y PUBMED. Se seleccionaron los trabajos científicos publicados en español, portugués o inglés entre 2000 y 2013 sobre la anemia ferropénica. Se identificaron y evaluaron un total de 102 estudios publicados entre el 1º de enero de 2000 y el 30 de junio de 2013. Cuarenta y dos artículos que reunían los criterios de inclusión (adolescentes con anemia) se seleccionaron para esta revisión. Finalmente, se realizó un análisis y se evaluaron los artículos de acuerdo con los objetivos del estudio.**

Resultados y discusión: **Los estudios revisados mostraron una prevalencia de anemia ferropénica cercana al 20 % en los adolescentes y describían los efectos deletéreos de la anemia en este grupo.**

Conclusión: **Se requiere una acción preventiva con respecto a la anemia ferropénica. Los profesionales sanitarios deberían ser conscientes de la necesidad de un diagnóstico, profilaxis y tratamiento precoces.**

(*Nutr Hosp.* 2014;29:1240-1249)

DOI:10.3305/nh.2014.29.6.7245

Palabras clave: *Anemia ferropénica. Déficit de hierro. Adolescente.*

Abbreviations

Hb: Hemoglobin.
HbA2: Hemoglobin A2.
Ht: Hematocrit.
MCV: Mean corpuscular volume.
RDW: Red cell distribution width.
WHO: World Health Organization.

Introduction

Anemia is a term given to a pathological process in which erythrocyte hemoglobin (Hb), hematocrit (Ht) and the concentration of red blood cells per unit of volume are abnormally low compared to the peripheral blood parameters of a reference population. In normal individuals, hematocrit and hemoglobin levels vary in accordance with the phase of development of the individual, and as a function of hormonal stimulation, environmental oxygen pressure, age and gender[1]. The cut-off hemoglobin limits established by the World Health Organization (WHO) to define iron deficiency anemia are shown in table I.

Iron deficiency

The amount of iron in the body varies according to weight, gender, hemoglobin level and the size of body iron stores[2]. Iron deficiency is defined by a reduction in ferritin levels that generally results from a diet in which the bioavailability of iron is inadequate or from an increased need for iron during a period of intense growth (pregnancy, adolescence and infancy). Decreased ferritin levels may also be the consequence of extensive blood loss, either in hemorrhagic conditions or in cases of occult bleeding[3,4], or following inflammatory processes caused by various chronic diseases.

Iron deficiency anemia

Iron deficiency anemia is the most advanced stage of iron deficiency. It is characterized not only by low hemoglobin and hematocrit levels but also by a reduction or depletion of iron stores, by low serum iron levels and decreased transferrin saturation[5]. In general, serum iron levels decrease in the presence of acute and chronic infections, extensive inflammatory processes, malignant neoplasms, during menstruation and, principally, when there is a prolonged deficit of iron in the diet. [6,7] High levels, on the other hand, may be a consequence of iron poisoning or may present during some types of hemolytic anemia, hemochromatosis and sideroblastic anemia[6,7].

Iron is known to play an important role in the formation of hemoglobin, myoglobin and other heme proteins. In the diet, iron is present in red meat, eggs, vegetables and grains. Its absorption depends largely on its balance in the body. Commonly, around 10% of iron intake is absorbed. Infants and children, particularly schoolchildren, need iron-rich diets for their growth, psychomotor development and intellectual capacity[6]. Evidence that iron deficiency hampers psychomotor development and cognitive function is attracting more and more interest. These alterations are particularly concerning, since they occur even in the presence of relatively mild anemia (Hb levels <11 g/dl) and their reversibility remains uncertain[8,9].

Table I
Hemoglobin cut-off levels for diagnosing anemia, in accordance with the 2001 World Health Organization definitions

Age Group and Gender	*Hemoglobin (g/dl)*
Children of 6 to 59 months (both sexes)	11.0
Children of 5 to 11 years (both sexes)	11.5
Children of 12 to 14 years (both sexes)	12.0
Non-pregnant women (> 15 years)	12.0
Pregnant women	11.0
Men (> 15 years)	13.0

Source: WHO, 2001[3]

Epidemiology

Anemia is considered the most common nutritional deficiency worldwide and in 95% of cases it is associated with an iron-poor diet[3], despite the fact that iron is the second most abundant metal in the earth's crust. Anemia is more common in infants, in children of 3 to 6 years of age and in adolescents of 11 to 17 years of age[10,11], particularly those living in developing countries, constituting a serious public health issue[3].

The World Health Organization estimates that around two billion individuals worldwide, i.e. over 30% of the world's population, are anemic, highlighting the importance of anemia as a public health issue in both developing and developed nations[12,13]. In developed countries, 4.3 to 20% of the population, depending on age and gender, are affected by iron deficiency anemia, while in developing countries these figures range from 30 to 48%[13]. Notwithstanding, few data are currently available on the prevalence of iron deficiency anemia in adolescents. Statistics published in the United States show iron deficiency prevalence rates of 9% in girls of 12 to 15 years of age and 16% in girls aged 16-19 years. In boys, these rates are lower[14].

A study conducted in Switzerland with teenagers showed a prevalence of anemia of 14.5% in girls and 7.9% in boys[15]. In other European countries such as Spain, Sweden and England, the prevalence of anemia in adolescents has been reported to be around 4.0%[16,17]. In developing countries, the situation is more serious. In India, a prevalence of anemia of 45% has been reported for teenage girls[18]. In Indonesia, prevalence

rates were 26% and 11% for girls and boys, respectively[19]. In Jamaica, anemia was identified in 25% of adolescents of 12 to 15 years of age. [13] More recent studies conducted in the city of Porto in Portugal revealed a prevalence of anemia of 2.6% in adolescents, with that rate being higher in girls (4.1%) compared to boys (1.0%)[20].

In Brazil, although a multicenter nationwide survey has yet to be conducted, there is a consensus within the scientific community that the prevalence of iron deficiency anemia is high throughout the entire country, affecting all social classes irrespective of the geographical region[21], with an estimated rate of anemia of 20% in adolescents[22]. Population-based studies in which the prevalence of anemia is compared in urban and rural areas show that the percentage of individuals with anemia is much higher in rural areas. It is estimated that around 50% of children in rural areas of Brazil have iron deficiency anemia[23], making this the most important nutritional deficiency in rural compared to urban areas of the country.

Risk factors for iron deficiency anemia

Adolescence is an important period of nutritional vulnerability due to the increased nutritional demands for growth and development during this phase. Iron requirement is high because of intense growth and muscle development, resulting in an increase in blood volume[24]. In adolescents, dietary iron intake may be poor as the result of inadequate intake at this particular time of life or the adolescent's diet may have been iron-poor since infancy; however, it is vital that there is an adequate level of iron in the diet with sufficient bioavailability to satisfy the body's demands during this particular time of life[24].

Another characteristic that is common among adolescents refers to a change in dietary habits resulting from peer influence, a need for self-affirmation within the family or as the result of the behavioral or social changes that teenagers face during this phase[25]. In this context, food also serves as a vehicle that is used to demonstrate feelings of rebelliousness and dissatisfaction, particularly in families in which dialogue is lacking. In adolescence, eating disorders may include a refusal to eat, excessive weight-loss diets and skipping meals, all because of the undue importance given to body image as a result of inappropriate advertising in the media and the cult of ultrathin, often malnourished models.

Another important aspect that should be taken into consideration refers to the consequences of current lifestyles, with increasing dependence on food that can be prepared rapidly and simply. Fast food is potentially harmful, since there are often important nutritional limitations with this type of food, including its high energy, fat and sodium content in conjunction with its poor fiber, vitamin, calcium and iron content[26]. Consequently, adolescents' diets are often based on inadequate socioeconomic and sociocultural values, a distorted body image, poor family eating habits, the financial situation of the family, food consumed outside the home, the availability, ease and speed of food preparation and the influence of peers and of the media. Most of these factors contribute to an iron-poor diet.

Factors that predispose to iron deficiency anemia

Iron deficiency anemia is the result of a protracted imbalance between iron intake and demand[2,3]. A great number of factors that predispose to iron deficiency have been mentioned in the literature, particularly early discontinuation of exclusive breastfeeding, lack of iron-rich foods in the diet, frequent tea consumption, prematurity, low birthweight, intrauterine growth restriction, twin pregnancies, perinatal bleeding, socioeconomic level, poor maternal schooling and poor basic sanitation and life conditions[2,11,27,28].

The most important factors determinin iron deficiency anemia

1. An inadequate diet, with poor iron, micronutrient and vitamin content, leading to an insufficient intake of nutrients such as iron, folic acid, vitamin A, vitamin B12 and vitamin D[29]. Multiple micronutrient deficiencies are still common worldwide and may be present at any age, hampering both physical and cognitive development[30].
2. The use of medication and food that inhibit iron absorption, including antacids, aspirin, nonsteroidal anti-inflammatory drugs, and excessive phytate, phosphate, oxalate and tannin intake[29].
3. Overweight and obesity. The prevalence of overweight and obesity has increased significantly in children and adolescents and, in these individuals, iron deficiency may be related to a micronutrient-poor, calorie-rich diet, to a greater need for iron that is associated with body weight, to genetic factors and/or to sedentariness[31,32]. Furthermore, overweight and obesity lead to a continuous inflammatory process, intensifying anemia and hampering treatment[33].
4. Malnutrition, when, in addition to an inadequate diet, there are other possible associated conditions such as malabsorption syndrome and/or excessive iron loss. In this context, these patients also have flattening or atrophy of the intestinal villi, hampering micronutrient absorption[34,35].
5. Another group that merits particular attention consists of adolescent athletes in whom the prevalence of iron deficiency ranges from 5 to 7.5%. In addition, they are predisposed to deve-

loping "sports anemia". This type of anemia appears to be associated with various factors including dilutional pseudoanemia, mechanical intravascular hemolysis and iron loss[22,36,37].

6. Iron deficiency caused by blood loss resulting from injury, accidents or blood donation (every 500 ml of blood donated per year results in the loss of another 0.5 mg of iron/day)[29].
7. Iron loss due to parasitosis of the gastrointestinal tract (*Entamoeba histolytica*, *Necator americanus*, *Ascaris lumbricoides*, *Schistosoma mansoni*, *Trichuris trichiura*)[38], esophagitis, angiodysplasia, telangiectasia, atrophic gastritis, colitis, *Helicobacter pylori* infection, coeliac disease[39,40], inflammatory bowel disease, diverticulosis, hemorrhoids, gastrectomy or gastroplasty (bariatric surgery), etc.[41-45]
8. Genitourinary iron loss of various etiologies[46], including paroxysmal nocturnal hemoglobinuria and glomerulonephritis.
9. Pregnancy, childbirth and the use of intrauterine devices.
10. Menarche and menstrual abnormalities in adolescents, in combination with an inadequate diet. Heavy menstrual bleeding is also a common cause of iron deficiency and iron deficiency anemia in women of reproductive age. In these cases, menstrual bleeding is moderate, but chronically heavier than normal, causing a negative iron balance[47,48]. Iron deficiency anemia is less common in adolescent boys than in girls and this is explained by the physiological increase in hemoglobin levels caused by sexual maturation. Nonetheless, iron deficiency may be higher in this age group due to blood volume expansion and the increase in muscle mass[38]. On the other hand, any increase in hemoglobin levels that might be expected in girls is offset by menstrual blood loss[49,50]. Other factors that may increase the risk of anemia and iron deficiency in girls include use of the intrauterine device, pregnancy and also childbirth[29,51].
11. The association between infection and anemia remains controversial; however, the reduction in hemoglobin levels during an infectious process is presumed to be the result of impaired iron release from the reticuloendothelial system and a consequent reduction in the amount of iron available for erythropoiesis[51].

Table II lists the most important factors responsible for iron deficiency anemia in adolescents.

The influence of hormones as a cause of anemia in adolescence

In adolescence, hemoglobin levels are admittedly higher in males than in females because prostaglandins (PGE) facilitate erythropoietic activity, both directly (PGE 1) and via cyclic AMP (PGE 2). Androgens stimulate erythropoietin action by increasing or facilitating its production in the erythroid stem cells. Conversely, estrogens inhibit the effects of erythropoietin[52].

Due to changes in the nutritional requirements of adolescents –at menarche in girls and as a result of the hormonal changes at puberty in boys– hemoglobin levels differ as a function of gender, age or stage of sexual maturity[12,53] (table I).

In women of reproductive age, menstrual bleeding defines anemia, sometimes requiring daily oral iron supplementation. Women in whom menstrual bleeding is excessive, either with respect to the number of bleeding days or to the amount of flow and the occurrence of menstrual clots, need to be monitored continuously for as long as dysfunctional uterine bleeding is present[47,54], a period in which iron supplementation may indeed be required.

Table II
The most important factors contributing to iron deficiency anemia in adolescents

Causes	*Peculiarities*
Iron-poor diet	Inappropriate dietary habits
Medication/food	Use of medication and foods that inhibit iron absorption
Overweight and obesity	Iron requirements are higher as a function of weight and iron-poor food
Malnutrition	Mucosal lesions of the duodenum prevent iron absorption
Iron deficiency associated with sporting activities	"Sports anemia"
Acute or chronic blood loss, injury, blood donation	Depletion caused by blood loss
Gastrointestinal tract disorders	Parasitosis, peptic disease, *H. pylori* infection, inflammatory bowel disease, coeliac disease, hemorrhoids, diverticulitis
Genitourinary losses	Paroxysmal nocturnal hemoglobinuria
Menarche and menstrual abnormalities	Metrorrhagia
Pregnancy, childbirth and use of an intrauterine device	
Chronic and acute diseases	

The physiopathology of iron deficiency anemia

The most important protein as far as iron reserves are concerned is ferritin, which is found in almost all the cells of the body, iron reserves being situated principally in organs such as the spleen, liver and bone marrow[55,56].

Serum ferritin level is the most accurate indicator of body iron stores[57]. Plasma ferritin levels decrease when there is a deficiency of iron that is not complicated by another concomitant disease. This reduction in ferritin occurs early, well before the abnormalities in hemoglobin levels, serum iron levels or in erythrocyte size become apparent. On the other hand, increased ferritin levels may occur in the presence of infections, neoplasms in general, and in cases of leukemia, lymphoma, breast cancer, renal disease, rheumatoid arthritis, hemochromatosis or hemosiderosis, as well as following alcohol consumption[55-57].

Serum ferritin, when used alone as a single parameter, is not considered a good indicator of the nutritional iron status of a population, since this measurement does not provide all the information necessary on the prevalence of anemia[27,28]. To reach a definitive diagnosis of iron deficiency anemia, in addition to performing a full blood count (hemoglobin, hematocrit, red blood cell count), ferritin and serum iron levels should be measured[27,58]. Iron is essential for most living creatures, since it plays a role in numerous vital processes ranging from cell oxidative mechanisms to oxygen transport to the tissues.

Iron homeostasis is regulated principally by iron absorption rather than excretion; therefore, serum iron level reflects the balance between the amount of iron absorbed and the amount used by the body[55,56]. Iron deficiency develops gradually and progressively until anemia is established[57,59] (table III). The first stage of anemia consists of iron depletion or a negative iron balance. It is characterized by a period of greater vulnerability (affecting iron stores) and may progress slowly to a more severe deficiency, with functional consequences. As iron stores deplete, ferritin levels fall, with iron values < 12 ng/ml corresponding to depleted iron stores[29].

The second stage, also referred to as "iron deficiency", is characterized by a phase of erythropoiesis. Iron is depleted, but anemia is not yet present, although biochemical abnormalities reflect its inability to produce hemoglobin normally. The transferrin saturation index is < 16% and there is an increase in red cell distribution width (RDW) of more than 16% and a reduction in mean corpuscular volume (MCV) < 80 fl, in the presence of populations of microcytic and hypochromic erythrocytes[2,4,29].

The third stage (iron deficiency anemia itself) is characterized by a reduction in iron delivery to the bone marrow, reducing both hemoglobin synthesis and content in erythrocyte precursor cells. The damage inflicted on the body increases as the concentration of available iron diminishes[2,29].

Diagnostic approach

To diagnose iron deficiency anemia, a full blood count must be performed and serum ferritin levels must be measured[57,58,60,61].

When iron is deficient, the body initially turns to its iron stores, consequently depleting them. It is at this stage that ferritin levels fall; however, there are no functional abnormalities at this point. Next, serum iron levels decrease, transferrin saturation diminishes and iron-binding capacity increases; however, anemia is not yet present. It is only when the negative iron balance persists that anemia develops or manifests itself[29,51].

Diagnosis is based on three different aspects: a complete history of the patient, focusing on possible signs and symptoms; a detailed physical examination, also taking the patient's sexual maturation into consideration; and laboratory tests.

In the majority of cases, the onset of anemia is insidious, with symptoms appearing gradually. The principal symptoms are pallor, fatigue, dyspnea on exertion, tachycardia, palpitations, physical debility, irritability, anorexia, headache, paresthesia, retarded growth, papillary atrophy of the tongue, koilonychia, cheilitis, swollen limbs, changes in appetite, mood changes,

Table III
Stages involved in the onset of iron deficiency

	Stage 1 *Depletion of iron stores*	*Stage 2* *Depletion of iron stores*	*Stage 3* *Depletion of iron stores*
Hemoglobin	Normal	Normal	Reduced
Mean corpuscular volume (MCV)	Normal	Normal	Reduced
Serum iron levels	Normal	Reduced	Reduced
Ferritin	Reduced	Reduced	Reduced
Iron-binding capacity	Normal	Increased	Increased
Free protoporphyrin	Normal	Normal	Increased

Source: Brazil - Ministry of Health, UNICEF[46].

attention disorders and poor school performance[62]. Less common symptoms associated with anemia include: major hemorrhage resulting from a range of different diseases or injuries that may lead to a state of shock and acute anemia.

Adolescence is a period of profound physical and psychological changes before adult life begins. Therefore, pediatricians should be attentive to a variety of physical, behavioral and social-related facets, in addition to the pathologies that tend to be characteristic of this period of life.

Pubertal staging allows the physician to establish the degree of maturity of his/her adolescent patient, to make correlations between different puberty-related phenomena, to estimate the probable time of menarche, the time of the growth spurt and final height. In addition, it enables the doctor to offer the adolescent prior guidance on the puberty-related events yet to come, to provide advice on selecting the most appropriate sporting activities for him/her, to interpret supplementary tests correctly and to treat the pathologies associated with puberty[63].

Sexual maturity can be staged by evaluating the breasts and pubic hair of girls and the external genitalia and pubic hair of boys. Breasts and male genitals are assessed in accordance with their size, shape and characteristics, while pubic hair is graded according to its characteristics, quantity and distribution (tables IV and V). Stage 1 always corresponds to pre-puberty and stage 5 to the post-pubertal adult phase. Therefore, stages 2, 3 and 4 characterize puberty. This classification system is generally known as the Tanner scale[1,63].

Clinical examination of the adolescent patient should take the Tanner scale into consideration (tables IV and V), remembering that the iron requirements of the adolescent increase during the pubertal growth spurt[64]. Peak growth occurs during Tanner stage 4 when there is extensive formation of muscle mass. In girls, menarche occurs at Tanner stage 4, a time when growth is already decelerating. During the first 2-3 years after menarche, menstrual cycles and bleeding are generally irregular due to the immaturity of the hypothalamic-pituitary-adrenal axis, with consequent iron loss[62].

The nutritional status of adolescents is important and should be evaluated according to their body mass index (BMI) and sexual maturation index[65] to enable timely identification of any nutritional disorders. Nutritional status should be evaluated systematically.

The initial laboratory workup for anemia consists of a complete blood count and reticulocyte count. An erythrocyte count of < 3.9 million/ml, together with hemoglobin levels < 12 g/dl in adolescent girls or < 12.5 g/dl in boys and hematocrit < 33%, confirms the hypothesis of anemia. In addition to these tests, red blood cell indices such as low MCV, increased coefficient of varia-

Table IV
Pubertal staging (boys): testicular volume (G) and pubic hair (P)

External genitalia (boys)	
G1	Prepubertal.
G2	Enlargement of scrotum and testes; scrotum skin reddens and changes in texture; slight or no increase in the size of the penis.
G3	Enlargement of penis (length at first); further growth of testes.
G4	Increased size of penis with growth in breadth and development of glans; testes and scrotum larger; scrotum skin darker.
G5	Adult genitalia.
Pubic hair (both sexes)	
P1	Prepubertal (presence of velus hair similar to abdominal wall).
P2	Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia.
P3	Darker, courser and more curled hair, spreading sparsely over junction of pubes.
P4	Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs.
P5	Adult in quantity and distribution, spreading to internal surface of the thighs.
P6	Spreading upwards over the pubis.

Table V
Pubertal staging (girls): breasts (B)

Breasts (girls)	
B1	Prepubertal.
B2	Breast bud stage with elevation of breast and papilla; enlargement of areola.
B3	Further enlargement of breast and areola; no separation of their contour.
B4	Areola and papilla form a secondary mound above level of breast.
B5	Mature stage: projection of papilla only, related to recession of areola.

tion of RDW and reticulocytopenia (< 0.5%) are suggestive of iron deficiency[37,66].

When iron deficiency is suspected, total body iron stores should be quantified. Alterations in serum iron levels are only detectable when iron stores have already been depleted. Levels of < 30 mcg/dl are indicative of low transferrin, an index with high sensitivity for iron deficiency whenever < 16%. Total iron-binding capacity and free erythrocyte protoporphyrin are above normal in the presence of iron deficiency[67,68].

Ferritin is the earliest indicator of iron deficiency and the one with highest specificity when levels are < 12 ng/ml[68,69] or < 15 ng/ml in adolescents[3]. Nevertheless, in infectious, inflammatory or malignant states, ferritin levels may be high, since it is an acute-phase reactant[67,68].

Therefore, although all these tests are useful, no single test is acceptable alone for a diagnosis of iron deficiency and, whenever possible, ferritin measurement should be given priority among the iron store markers.

Various other tests may help lead to a diagnosis of anemia, including iron-binding capacity, transferrin saturation, free erythrocyte protoporphyrin, transferrin receptors and also bone marrow testing, which, although useful for establishing a diagnosis of iron deficiency anemia, is only used when diagnosis proves difficult and all other methods have already been attempted[70,71].

Evaluation of the gastrointestinal tract in patients with iron deficiency anemia

Evaluation of the gastrointestinal tract forms an integral and obligatory part of the investigation of any patient of any age with iron deficiency anemia. The principal tests used to investigate the digestive tract are a fecal occult blood test, upper gastrointestinal endoscopy and colonoscopy. In the case of patients whose results are normal in all of these tests, others such as labeled erythrocyte scintigraphy, angiography and capsule endoscopy may be performed[5,8,11]. It is important to bear in mind that iron refractory iron deficiency anemia may occur as a symptom of coeliac disease. It should also be remembered that anemia may occur in patients with gastroesophageal reflux disease, in food allergies and in inflammatory bowel disease.

Although the finding of upper digestive tract abnormalities at endoscopy is common and includes esophagitis, gastritis and hiatus hernia, in many cases, these conditions do not, on their own, explain the presence of iron deficiency. On the other hand, colonoscopy may reveal infectious or inflammatory processes, polyps or neoplastic causes[8].

It is important to confirm the patient's clinical history, verifying whether he/she is in use of acetylsalicylic acid, anti-inflammatory drugs or anticoagulants, and whether they have a history of abnormal bleeding so that a possible diagnosis of coagulopathy (for example, von Willebrand disease) can be investigated[29,51].

Differential diagnosis of microcytic anemia

The most important differential diagnosis in patients with iron deficiency anemia is beta-thalassemia minor. In beta-thalassemia minor, red blood cell count is either normal or elevated, RDW is < 18% and there is an increase in hemoglobin A2 (HbA2)[70].

When thalassemia minor is associated with iron deficiency anemia, HbA2 measurement is affected and levels are lower. Therefore, if this association is suspected, total body iron stores should be corrected prior to measuring HbA2. Serum ferritin < 12 ng/ml practically confirms iron deficiency anemia, whereas values > 100 ng/ml essentially exclude this diagnosis even in the presence of an inflammatory condition or liver disease.

Another differential diagnosis for iron deficiency anemia is anemia of chronic disease. In this situation, hemoglobin values normally fluctuate between 9 and 11 g/dl. In general, this type of anemia is asymptomatic or oligosymptomatic and is associated with the presence of an inflammatory or infectious disease or with neoplasia. Usually, it is a normochromic and normocytic form of anemia; however, it may be microcytic and hypochromic. Serum iron levels and transferrin saturation are low; nevertheless, ferritin is normal or elevated, with normal or high levels of iron in bone marrow[5,11,31,36].

Prevention

Prevention of iron deficiency anemia should be based on four approaches:

1. Nutritional counseling aimed at improving the quality of the diet. Breastfeeding should be encouraged;
2. Iron supplementation therapy;
3. Fortification of food;
4. Infection control.

Providing dietary counseling is fundamental and it is important to explain that the bioavailability of iron obtained from meat (red or white meat) is greater. In addition to meat, individuals should be encouraged to consume citric fruits, vegetables and legumes and be warned to avoid sodas, tea, coffee, excessive amounts of milk, and cereals that reduce iron absorption[51].

Primary prevention of iron deficiency in adolescents is not recommended. Some investigators defend the prescription of iron supplements to adolescents as secondary prevention due to the high prevalence of iron deficiency in this population, particularly in girls[69] and in athletic teenagers. The American Academy of Pediatrics recommends that adolescent girls should be followed up annually after menarche and boys should be monitored during their growth spurt to identify anemia.

In Brazil, the Ministry of Health decreed that all wheat and corn flour produced from July 2004 onwards

should be supplemented with iron[52]. Other foods such as milk are also fortified with iron, which helps to prevent anemia[72].

Therefore, bearing in mind the differences of opinion with respect to the prevention of iron deficiency anemia in adolescents, this decision should be individualized in accordance with the risk factors present in this population, which include low socioeconomic status, malnutrition, obesity, intense physical activity, an iron-poor diet, chronic disease or a history of menstrual blood loss > 80 ml/month. Adolescents in these categories should be screened and a full blood count and ferritin measurement should be performed[73,74].

Treatment

Forms of iron supplementation and its benefits

Iron deficiency and its many consequences can be corrected simply, cheaply and effectively. The most common approach is to provide iron supplements to pregnant and breastfeeding women and to breastfeeding infants within a primary healthcare program. Despite the confirmed efficacy of these programs, their effectiveness is sometimes very low. The principal objective of dietary interventions is to increase the body's iron stores[75].

Supplementation therapy

Iron supplements should be prescribed to all patients with a diagnosis of anemia, since dietary changes alone are unable to correct iron deficiency anemia. Oral supplementation is the modality of choice, with parenteral administration being reserved for patients unable to tolerate oral supplements[75].

Iron salts (ferrous sulfate, fumarate and gluconate) are highly bioavailable, rapidly absorbed and inexpensive. Since absorption of these salts is hampered by food, they should be taken one hour before meals. On the other hand, they may provoke gastrointestinal side effects such as diarrhea, epigastric pain, nausea and constipation[51].

Therapies with ferrous salts and iron chelates are effective and cause few side effects. Furthermore, their absorption is unaffected by food; therefore, they can be taken either fasting or during meals. Their major drawback is cost.

The treatment dose depends on the severity of the anemia. For infants, the recommended dose is 4-5 mg/kg/day of elemental iron. For adolescents and adults, the dose is 60 mg of elemental iron twice a day in the case of moderate anemia[76]. Treatment should result in an increase in hemoglobin levels of 1.0 g/dl in a month. After hemoglobin levels return to normal, treatment should be maintained using the same dose for at least 4-8 weeks so as to replenish the body's iron stores[51]. Blood transfusions are rarely required and are restricted to severe cases in which there is a significant loss of blood and a risk of cardiac decompensation[51]. Iron-fortified foods are important and several studies have been published showing their effectiveness[77,78].

Controlling infections is important, since iron is also reduced in chronic diseases and this may result in an erroneous diagnosis of iron deficiency anemia. Gastrointestinal and respiratory tract infections are known to predispose to a depletion of iron stores in the body due to diminished hemoglobin production and iron absorption[70,79].

Conclusion

In view of the magnitude of this problem and the number of risk factors involved, urgent and systematic measures need to be taken to prevent and treat iron deficiency anemia in adolescents.

Iron deficiency anemia is common worldwide. It is estimated that 25% of the population is affected by iron deficiency and the most common groups affected are children of 4-24 months of age, schoolchildren, adolescent girls, and pregnant and breastfeeding women[80]. Studies show a high prevalence of around 20% of iron deficiency anemia in adolescents[81].

Fortifying food with iron is the most effective measure for combatting iron deficiency in a population, since this strategy extends to all socioeconomic groups. The use of fortified milk formulas has contributed towards a decline in iron deficiency in infants of various countries. In Brazil, the most extensive experience has been with the use of fortified milk, in powdered or liquid form, with results that have proven satisfactory both for the prevention and treatment of anemia[77,80].

Iron deficiency anemia remains a major public health issue in Brazil despite all the knowledge available on intervention measures. Various research studies have published excellent results with the establishment of preventive measures or treatment such as iron-fortified foods and iron supplements, measures that should always be implemented in conjunction with dietary counseling[20,82].

The ideal strategy is to treat prophylactically and to recognize those individuals at risk of developing anemia as early as possible to prevent onset of the disease and its complications. Therefore, educating healthcare professionals to implement preventive strategies, to treat infections and to detect iron deficiency and anemia at an early stage is vital[50].

Few population-based studies have been conducted in Brazil specifically on iron deficiency anemia in adolescents; therefore, there is a need for a greater in-depth analysis of dietary habits and anemia in this age group in the different geographical regions of the country.

References

1. Jordão RE, Bernardi JLD, Barros Filho AA. [Prevalence of iron-deficiency anemia in Brazil: a systematic review]. *Rev Paul Pediatr* 2009; 27 (1): 90-8.
2. Braga JAP. O papel do ferro no crescimento e desenvolvimento infantil. O papel dos micronutrientes no crescimento e desenvolvimento infantil. São Paulo: SARVIER; 2008. pp. 48-645.
3. World Health Organization. Iron deficiency, anaemia assessment, prevention, and control. A guide for programme managers. Geneva; 2001. [cited 2012 Feb 1]. Available from: http://www.who.int/entity/nntrition/publications/micronutrients/anaemia.iron_deficiency/ en/ida_assessment_ prevention_ control.pdf.
4. Bortolini GA. Anemia ferropriva. Nutrição da gestação ao envelhecimento. Rio de Janeiro: Rubio; 2008. p. 243-59.
5. Braga JAP, Taddei JA. Anemias carenciais. Nutrição em saúde pública. Rio de Janeiro: Rubio; 2011. p. 197-209.
6. Cohen A, Schwartz E. Iron chelation therapy in sickle cell anemia. *Am J Hematol* 1979; 7 (1): 69-76.
7. Cook JD. Newer aspects of the diagnosis and treatment of iron deficiency. American Society of Hematology Educational Program Book; 2003. p. 40-61.
8. Zago MA, Falcão RP, Pesquini R. Hematologia: fundamento e prática. São Paulo: Atheneu; 2004.
9. Carter RC, Jacobson JL, Burden MJ, Armony-Sivan R, Dodge NC et al. Iron deficiency anemia and cognitive function in infancy. *Pediatrics* 2010; 126 (2): e427-34.
10. Andrews NC. Intestinal iron absorption: current concepts circa 2000. *Dig Liver Dis* 2000; 32 (1): 56-61.
11. Looker AC, Dallman PR, Caroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA* 1997; 277 (12): 973-6.
12. Silva FC, Vitalle MSS, Quaglia EC, Braga JAP, Medeiros EHGR. Proporção de anemia de acordo com o estadiamento puberal, segundo dois critérios diagnósticos. *Rev Nutr Campinas* 2007; 20 (3): 297-306.
13. Centers for Disease Control and Prevention (CDC). Iron deficiency, United States, 1999-2000. *MMWR Morb Mortal Wkly Rep* 2002; 51 (40): 897-9.
14. Nunes SMT, Yuyamada LKO, Guedes DP, Oliveira MC. Anemia ferropriva em atletas adolescentes da Fundação Vila Olímpica de Manaus-AM. *Acta Amaz* 2008; 38 (2): 263-6.
15. Massawe SN, Ronquist G, Nyström L, Lindmark G. Iron status and iron deficiency anaemia in adolescents in a Tanzanian suburban area. *Gynecol Obstet Invest* 2002; 54 (3): 137-44.
16. Caballo Roig N, Garcia P, Valdemoro M, del Castillo ML, Santos Tapia M, González Vargaz A et al. [The prevalence of anemia in the children and adolescents of Madrid]. *An Esp Pediatr* 1993; 39 (3): 219-22.
17. Nelson M, White J, Rhodes C. Haemoglobin, ferritin, and iron intakes in British children aged 12-14 years: a preliminary investigation. *Br J Nutr* 1993; 70 (1): 147-55.
18. Das DK, Biswas R. Nutritional status of adolescent girls in a rural area of North 24 Parganas district, West Bengal. *Indian J Public Health* 2005; 49 (1): 18-21.
19. Soekarjo DD, Pee S, Kusin JA, Schreurs WH, Schultink W, Muhilal et al. Effectiveness of weekly vitamin A (10,000 IU) and iron (60 mg) supplementation for adolescent boys and girls through schools in rural and urban East Java, Indonesia. *Eur J Clin Nutr* 2004; 58 (6): 927-37.
20. Moreira ICM. Anemia em adolescentes, prevalência e factores associados: o papel do *Helicobacter pylori*. (Tese de mestrado). Universidade do Porto, Faculdade de Medicina, Instituto de Ciências Biomédicas Abel Salazar; 2010.
21. Bagni UV, Veiga GV. Anemia ferropriva e obesidade: novos olhares para antigos problemas. *Nutrire* 2011; 36 (1): 177-88.
22. Soekarjo DD, de Pee S, Bloem MW, Tjiong R, Yip R, Schreurs WH et al. Socio-economic status and puberty are the main factors determining anaemia in adolescent girls and boys in East Java, Indonesia. *Eur J Clin Nutr* 2001; 55 (11): 932-9.
23. Iuliano BA, Frutuoso MFP, Gambardella AMD. Anemia em adolescentes segundo maturação sexual. *Rev Nutr Campinas* 2004; 17 (1): 37-43.
24. Mesías M, Seiquer I, Navarro MP. Iron nutrition in adolescence. *Crit Rev Food Sci Nutr* 2013; 53 (11): 1226-37.
25. Nathan GD, Orkin SH. Appendices - Reference values in infancy and childhood. In: Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE, editors. Nathan and Oski's hematology of infancy and childhood, 5th ed. Philadelphia: WB Saunders; 1998.
26. Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE. Nathan and Oski's hematology of infancy and childhood. 7th ed. Philadelphia, PA: Saunders; 2009. pp. 911-1015.
27. Schimitz BAS, Picanço MR, Aquino KKN, Bastos J, Giorgi E, Cardoso R et al. Prevalência de desnutrição e anemia em pré-escolares de Brasília - Brasil. *Pediatria Moderna* 1998; 34 (4): 155-64.
28. Neuman NA, Tanaka OY, Szarfarc SC, Guimarães PRV, Victora CG. [Prevalence and risk factors for anemia in Southern Brazil]. *Rev Saúde Pública* 2000; 34 (1): 56-632.
29. Reeves JD, Yip R, Kiley VA, Dallman PR. Iron deficiency in infants: the influence of mild antecedent infection. *J Pediatr* 1984; 105 (6): 874-9.
30. Kurpad AV, Edward BS, Aeberli I. Micronutrient supply and health outcomes in children. *Curr Opin Clin Nutr Metab Care* 2013; 16 (3): 328-38.
31. Nead KG, Halterman JS, Kaczorowski JM, Auinger P, Weitzman M. Overweight children and adolescents: a risk group for iron deficiency. *Pediatrics* 2004; 114 (1): 104-8.
32. Merckel D, Huerta M, Grotto I, Blum D, Tal O, Rachmilewitz E et al. Prevalence of iron deficiency and anemia among strenuously trained adolescents. *J Adolesc Health* 2005; 37 (3): 220-3.
33. Hoffbrand AV, PAH Moss, Pettit JE. Fundamentos em Hematologia. 5ª ed. Artmed: São Paulo; 2006.
34. Rockey DC. Occult gastrointestinal bleeding. *Gastroenterol Clin North Am* 2005; 34 (4): 699-718.
35. Braga JAP, Vitalle MSS. [Iron deficiency in infants and children]. *Rev Bras Hematol Hemoter* 2010; 32 (Supl. 2): 38-44.
36. Olsson KS, Marsell R, Ritter B, Olander B, Akerblom A, Ostergård H et al. Iron deficiency and iron overload in Swedish male adolescents. *J Intern Med* 1995; 237 (2): 187-94.
37. Oski FA. Iron deficiency in infancy and childhood. *N Engl J Med* 1993; 329 (3): 190-3.
38. Michaca VJS, Galaviz JLG, Pasillas MV, Huerta SF, Martinez LB, Monroy JVO, et. al. Consenso Nacional para el diagnóstico y tratamiento de la anemia em la infancia y em la adolescencia. *Pediatria de México* 2012; 14 (2): 71-85.
39. Brittenham GM. Disorders of iron metabolism: deficiency and overload. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, editors. Hematology: basic principles and practice. 2n ed. New York, NY: Churchill Livingstone; 1995: 492–523.
40. Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999; 341 (26): 1986-95.
41. Cançado RD, Chiattone CS. Aspectos atuais do metabolismo do ferro. *Arquivos Médicos dos Hospitais e da Faculdade de Ciências Médicas da Santa Casa de São Paulo* 2001; 46: 10-6.
42. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. *Mayo Clin Proc* 2003; 78 (10): 1274-80.
43. Milman N, Kirchhoff M. Influence of blood donation on iron stores assessed by serum ferritin and haemoglobin in a population survey of 1433 Danish males. *Eur J Haematol* 1991; 47 (2): 134-9.
44. Chiattone CS. Avaliação prospectiva de variáveis hematológicas em pacientes portadores de úlcera péptica submetidos a ressecção gástrica [tese]. São Paulo: Escola Paulista de Medicina; 1988.
45. Baker WF Jr. Iron deficiency in pregnancy, obstetrics and gynecology. *Hematol Oncol Clin North Am* 2000; 14 (5): 1061-77.
46. Brasil - Ministério da Saúde, Unicef. Carências de micronutrientes. Cadernos de Atenção Básica – nº 20. Série A. Normas e Manuais Técnicos. Brasília, DF: Ministério da Saúde; 2007.
47. Ballard L, Lyon DS, Jones JL. Patients with menometrorrhagia: etiologies, treatments, and outcomes. *South Med J* 2000; 93 (6): 571-4.
48. Rybo G, Leman J, Tibblin R. Epidemiology of menstrual blood loss. In: Baird DT, Michie EA, editors. Mechanisms of menstrual bleeding. New York: Raven Press; 1985. p. 181.

49. Pinhas-Hamiel O, Newfield RS, Koren I, Agmon A, Lilos P, Phillip M. Greater prevalence of iron deficiency in overweight and obese children and adolescents. *Int J Obes Relat Metab Disord* 2003; 27 (3): 416-8.
50. Santos CLA, Akerman M, Faccenda O, Martins LC, Reato LFN. Iron deficiency during pubertal growth spurt. *Rev Bras Crescimento Desenvolv Hum* 2012; 22 (3): 341-7.
51. Torres MA, Lobo NF, Sato K, Queiroz SS. [Fortification of fluid milk for the prevention and treatment of iron deficiency anemia in children under 4 years of age]. *Rev Saude Publica* 1996; 30 (4): 350-7.
52. Temoteo TL. Diagnóstico de anemia e fatores determinantes em escolares da rede pública de ensino de Teresina. Universidade Federal de Piauí - UFPI. Pro Reitoria de Pesquisa e Pós-Graduação, PRPPG Programa de Pós-Graduação em Alimentos e Nutrição - PPGAN. Tese de Mestrado; 2012.
53. Vitalle MSS. Perspectivas históricas. In: Braga JAP, Amancio OMS, Vitalle MSS. O ferro e a saúde das populações. São Paulo: Roca; 2006. p. 1-7.
54. Dallmann PR, Reeves JD. Laboratory diagnosis of iron deficiency. In: Stekel A, editor. Iron nutrition in infancy and childhood. Nestle Nutrition Workshop Series, 4. New York: Raven Press; 2001. p. 11-44.
55. Worwood M. The laboratory assessment of iron status –an update. *Clin Chim Acta* 1997; 259 (1-2): 3-23.
56. Gottschalk R, Wigand R, Dietrich CF, Oremek G, Liebisch F, Hoelzer D et al. Total iron-binding capacity and serum transferrin determination under the influence of several clinical conditions. *Clin Chim Acta* 2000; 293 (1-2): 127-38.
57. Paiva AA, Rondó PHC, Guerra-Shinohara EM. Parameters for the assessment of iron status. *Rev. Saúde Pública* 2000; 34 (4): 421-6.
58. Silva GD, Franceschini CSC, Priori SE, Ribeiro SMR, Lima NMM, Maffia UCC. Anemia ferropriva em crianças de 6 a 12 meses atendidas na rede pública de saúde do município de Viçosa, Minas Gerais. *Rev Nutrição* 2002; 12 (1): 54-9.
59. Assunção MC, Santos IS. [Effect of food fortification with iron on childhood anemia: a review study]. *Cad Saude Publica* 2007; 23(2): 269-81.
60. Longo KH. Aporte dietético de leite enriquecido com ferro aminoácido quelato em crianças com anemia ferropriva [monografia]. Erechim, RS: Faculdade de Farmácia, Universidade Regional Integrada (URI), Campus de Erechim; 2005.
61. Aguiar CD. Perfil hemoglobínico pós-suplementação com leite fortificado com ferro em crianças anêmicas em Erechim/RS [monografia]. Erechim, RS: Universidade Regional Integrada (URI), Campus de Erechim; 2006.
62. Biscegli TS, Corrêa CEC, Romera J, Cândido AB. [Nutritional status and iron deficiency among children enrolled in a day care center before and after 15 months of nutritional management]. *Rev Paul Pediatr* 2008; 26 (2): 124-9.
63. Marques MF, Marques MM, Xavier ER, Gregório EL. Fortificação de alimentos: uma alternativa para suprir as necessidades de micronutrientes no mundo contemporâneo. *HU Revista, Juiz de Fora* 2012; 38 (1): 78-86.
64. Sociedade Brasileira de Pediatria - SBP. Avaliação nutricional da criança e do adolescente: manual de orientação. 2009. [cited 2012 Feb 4]. Available from http://www.sbp.com.br/pdfs/MANUAL-AVAL-NUTR2009.pdf.
65. World Health Organization. Growth reference data for 5-19 years, WHO reference 2007. Available from: www.who.int/growthref/en/
66. Tran TN, Eubanks SK, Schaffer KJ, Zhou CY, Linder MC. Secretion of ferritin by rat hepatoma cells and its regulation by inflammatory cytokines and iron. *Blood* 1997; 90 (12): 4979-86.
67. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet* 1996; 348 (9033): 992-6.
68. Bourroul MLM, Scaramuzzi DR, Ferrer APS. Anemia na infância. In: Sucupira ACSL, Bricks LF, Kobinger MEBA, Saito MI, Zucolotto SMC. Pediatria em consultório. São Paulo: Sarvier; 2000.
69. Yip R, Walsh KM, Goldfarb MG, Binkin NJ. Declining prevalence of anemia in childhood in a middle-class setting: a pediatric success story? *Pediatrics* 1987; 80 (3): 330-4.
70. Hershko C. Iron, infection and immune function. *Proc Nutr Soc* 1993; 52 (1): 165-74.
71. Means RT. Iron deficiency anemia. *Hematology* 2013; 18 (5): 305-6.
72. Silva APR, Camargos CN. [Food fortification: efficient implement for fighting iron deficiency anemia?] *Comum Ciênc Saúde* 2006; 17 (1): 53-61.
73. Green M. Bright futures: national guidelines for health supervision of infants, children, and adolescents. VA National Center for Education in Maternal and Child Health, Arlington; 1994.
74. Braga JAP, Campoy FD. Anemia ferropriva. In: Braga JAP, Tone LG, Laggeto SR, editores. Hematologia para o pediatra. São Paulo: Atheneu; 2007. pp. 23-35.
75. Gillespie S, Kevany J, Mason J. Controlling iron deficiency. Geneva: United Nations/ Administrative Commitee on Coordinations/ Subcommittee on Nutrition; 2001.
76. Lewis SM, Bain B, Bates I. Hematologia prática de Dacie e Lewis. 9ª ed. Porto Alegre: Artmed; 2006.
77. Vitalle MSS. Crescimento e maturação sexual. In: Vitalle MSS, Medeiros EHGR. Adolescência: uma abordagem ambulatorial. Barueri: Manole; 2007.
78. Baker RD, Greer FR; Committee on Nutrition, American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics* 2010; 126 (5): 1040-50.
79. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; 44 (235): 291-303.
80. Queiroz SS, Torres MAA. Anemia ferropriva na infância. *J Pediatr* 2000; 76 (Supl. 3): S298-304.
81. Brazil - Ministério da Saúde. 2004. Compromisso social para a redução da anemia por carência de ferro no Brasil. 9 p. [cited 2012 Mar 23]. Available from http://dtr2004.saude.gov.br/nutricao/ferro.php.
82. Chipkevitch E. [Clinical assessment of sexual maturation in adolescents]. *JPED* 2001; 77 (Supl. 2): S135-42.