



ORIGINAL ARTICLE

Anemia in infancy: etiology and prevalence

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Abstract

Objective: to verify the prevalence of anemia, iron deficiency anemia and iron deficiency in infants, at a Public Health Unit in the city of Goiânia - Brazil; to analyze and to correlate the hematologic and biochemical variables.

Methods: a cross-sectional study was carried out. One hundred and ten full-term infants of the 120 mothers interviewed were included. The infants aged between six and twelve months and there were not twins. Socioeconomic and hematologic data was obtained. Venous blood was taken from fasting infants in order to carry out a complete hemogram through electronic cell counting, serum iron, serum ferritin and C-reactive protein, which were used in the evaluation of the etiology of iron deficiency in the anemic infants. Children with hemoglobin < 11g/dL were considered anemic.

Results: the prevalence of anemia was 60.9%. In the diagnosis of the iron deficiency etiology in infants without an inflammation process, when considering the alteration of hemoglobin plus two more indices among mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH) or serum ferritin or serum iron, the prevalence of the iron deficiency was 87%. Nevertheless, when red cell distribution width (RDW) was included in the indices, the prevalence was 97.8%. In the non-anemic infants, considering ferritin and RDW, the prevalence of iron deficiency observed was 28%. The best correlation among hematologic and biochemical variables were between hemoglobin and hematocrit ($r = 0.946$), and MCH with MCV ($r = 0.950$).

Conclusions: the main etiology in infants was iron deficiency anemia and its prevalence varied according to different parameters and criteria.

J Pediatr (Rio J) 2002; 78 (4): 321-6: iron deficiency anemia, nutritional status, iron, epidemiologic factors, infant, acute-phase proteins.

Introduction

Children between the ages of six and 24 months are among the most vulnerable to iron deficiency anemia, with the greatest risk being between six and twelve months, when complementary feeding has begun.

Iron deficiency may cause skin, mucosal and gastrointestinal abnormalities, low weight for age, reduced capacity for work and reduced immune response.^{1,2} Anemia also compromises physical, motor, psychological, behavioral, cognitive and language development.^{3,4}

Iron deficiency develops in three stages. Firstly, there is a reduction in serum ferritin, which is directly related to iron reserves.⁵ Secondly, a reduction in serum iron concentration and an increase in iron binding capacity. The third stage occurs with restriction in the synthesis of hemoglobin, which may lead to anemia.^{1,5} In iron deficiency anemia, red cells undergo morphological change from normocytic and normochromic to microcytic and hypochromic.¹

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Electronic cell counting allows analysis of hematimetric indices, which are important in the differential diagnosis of anemia. Low mean corpuscular volume (MCV) together with anemia favors diagnosis of iron deficiency anemia, as MCV obtained electronically is accurate and highly reproducible. Mean corpuscular hemoglobin (MCH) is also abnormal in iron deficiencies.⁵

In infants, low hemoglobin together with MCV below 72 fl and/or MCH below 24 pg suggests iron deficiency.^{6,7} Inadequate iron intake results in anisocytosis, where the erythrocytes produced are of small average size and large size variation. Anisocytosis is measured by red cell distribution width (RDW). Iron deficiency anemia thus leads to precocious increase in RDW, allowing early detection of iron deficiency before a large reduction in MCV occurs.^{8,9} Ferritin allows a quantitative analysis of the body's iron stores. Ferritin concentration below 10 or 12 ng/mL is considered indicative of iron depletion at all ages.^{5,7,10,11}

A number of tests can be used to evaluate iron deficiency: hemoglobin, hematocrit, ferritin, transferrin saturation, erythrocyte protoporphyrin, serum iron,¹¹⁻¹⁴ iron binding capacity, MCV, MCH, mean corpuscular hemoglobin concentration (MCHC), RDW,¹⁴ circulating serum transferrin receptor and reticulocyte hemoglobin content.¹⁵ As many of these tests lack specificity, a number of them are used together in the evaluation of types of anemia and the differential diagnosis of microcytosis.¹⁴

Infections and inflammations increase serum ferritin by two to four times, reducing its diagnostic value,¹⁰ as ferritin is a positive reactant in the acute phase.^{16,17} It is therefore important to exclude infants with these conditions by means of C-reactive protein (CRP), which is one of the acute phase proteins whose concentration also increases rapidly in case of infections and inflammations, allowing them to be detected before clinical diagnosis.^{16,18}

Venous blood gives greater reproducibility of results and diagnostic security for anemia than does capillary blood.^{5,7,19,20} Nonetheless, there is little research in Brazil using venous blood from term infants to evaluate the etiology of anemia and analyze biochemical and hematological variables. Sigulem *et al.* make reference to venipuncture.²¹

This study was carried out in the pediatric outpatients ward of a public health unit in the city of Goiânia, central Brazil, with the aim of establishing the prevalence of anemia, iron deficiency anemia and iron deficiency in infants between six and twelve months of age, comparing the use of two or more parameters in the diagnosis of iron deficiency anemia and analyzing and correlating the biochemical and hematological variables.

Methods

The study was observational and historical in nature, with cross-sectional epidemiological design. It was approved

by the Ethics and Research Committees of the Hospital das Clínicas of the Federal University of Goiás and the Hospital São Paulo, Federal University of São Paulo.

One hundred and twenty mothers were interviewed, and 110 infants included in the study. These infants were non-twins born at term, between six and twelve months of age (69 between six and nine months and 41 between nine and twelve months), not using iron sulfate and attending the pediatric outpatients ward. Infants with diarrhea were excluded as reduced plasmatic volume leads to a false erythrocytosis, obscuring early signs of anemia.⁸

A pilot study was carried out, with socioeconomic and hematological data collected between November 1997 and May 1998, after parents' informed consent was obtained. Per capita income expressed in US dollars was calculated on the basis of the minimum wage (R\$120.00 per month) and the average month-end exchange rate (US\$ 1.0 = R\$1.1304) during the collection period.

Eight mL of venous blood was collected after fasting to perform full hemogram, serum iron, ferritin and CRP tests at the clinical laboratory of the Hospital das Clínicas of the Federal University of Goiás.

Hemoglobin concentration was determined by electronic count, using Abbott Cell-Dyn 3000 equipment. MCV, MCH and RDW were also evaluated. Serum iron was evaluated using the enzymatic-colorimetric test on Merck Mega equipment. Ferritin was evaluated using the automated chemiluminescence assay on Immulite equipment. Serum CRP was evaluated using the latex agglutination test. CRP ≥ 6 mg/l indicates infection or inflammation. Anemic infants with temperature $\geq 37.5^\circ\text{C}$ and CRP ≥ 6 mg/l were excluded from analysis of iron deficiency etiology, as were those for whom results were not obtained for all parameters.

Children with hemoglobin less than 11 g/dL were considered anemic, following WHO guidelines (1968).²² Besides hemoglobin, iron deficiency etiology in anemic infants was evaluated using the lower normal limits for hematocrit (32%), MCV (72 fl), MCH (24 pg), serum iron (50 mg/dL)²³ and ferritin (10 ng/mL).⁷ RDW greater than 14.5% was taken to indicate iron deficiency, as recommended for children from one to five years.^{14,24}

Data were analyzed on Epi-Info 6.0225 and Sigma Stat for Windows 2.0 software, using the following statistical methods: chi-square test, Student's t test, Mann-Whitney test, Spearman correlation coefficient and analysis of sensitivity and specificity. Significance was established at 5%.

Results

Study group characteristics and socioeconomic conditions

Among the 110 infants studied, 54 were male, and 56 female. There was no significant difference in distribution by sex in the age groups six to nine months ($n = 69$) and nine

to twelve months ($n = 41$) ($P = 0.657$). There was also no significant difference between anemic and non-anemic infants in relation to age group ($P = 0.413$) or sex ($P = 0.128$).

Among the anemic infants, 62.7% were from families with per capita income below one minimum wage, that is, US\$ 106.16 per month. There was no significant relationship between anemia and per capita family income among infants from six to twelve months ($P = 0.770$). There was also no significant difference in proportion of anemic infants among children of mothers above and below median level of schooling (sixth grade) ($P = 0.926$).

Prevalence of anemia

Observed prevalence of anemia was 60.9% (Table 1), with 95% confidence of error within 9% absolute. Median, standard deviation and 95% confidence interval of hematological test results are presented in Table 2. Significant differences were found between anemic and non-anemic groups in terms of erythrocytes ($P < 0.001$), MCV ($P < 0.001$), MCH ($P < 0.001$) and MCHC ($P < 0.001$).

Table 1 - Infants of the anemic and non-anemic groups, both male and female, according to age group, Goiânia, 1998

Age group	Anemia		Total	Proportion of anemic infants (%)
	Yes	No		
6 9	40	29	69	58.0
9 12	27	14	41	65.9
Total	67	43	110	60.9

$\chi^2_{\text{calc}} = 0.67$ not significant.

Table 3 shows significant differences between anemic and non-anemic groups in terms of hematocrit ($P < 0.001$), RDW ($P = 0.012$), serum iron ($P < 0.001$) and ferritin ($P < 0.001$). Hemoglobin < 11 g/dL is therefore an adequate cutoff point for diagnosis of anemia.

Prevalence of iron deficiency anemia and iron deficiency

Table 4 shows the variations in prevalence of iron deficiency anemia according to the criteria adopted. It was found that when a second parameter was used (MCV, MCH, ferritin or serum iron) including RDW or not, iron deficiency prevalence reached 97.8%.

Using hemoglobin and RDW, anemia prevalence was 89.1%. When hemoglobin and two other parameters were used (not including RDW), prevalence was 87.0%. When RDW was included, prevalence was 97.8%. RDW increased the sensitivity of iron deficiency detection, as well as allowing the differential diagnosis of iron deficiency anemia and thalassemia.

Iron reserve depletion was 20% in 35 infants defined as non-anemic by ferritin level, and 28% in 32 infants defined as non-anemic by ferritin level and RDW. Abnormal CRP was found in 23% and 10% of anemic and non-anemic infants with normal temperature, respectively.

Correlation between biochemical and hematological variables

As shown in Table 5, there was no correlation between erythrocyte numbers and RDW ($r = 0.134$) or serum iron ($r = 0.044$). Correlation was found with the other biochemical and hematological variables. Hemoglobin showed the best correlation with hematocrit ($r = 0.946$), and MCH showed the best correlation with MCV ($r = 0.950$) and ferritin ($r = 0.634$).

Table 2 - Mean (M), standard deviation (SD) and confidence interval (CI) of 95% of the parameters: hemoglobin (Hb), n. of erythrocytes (n. erythr.), mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), of the anemic and non-anemic groups

Parameters*	Anemia				Student <i>t</i> test	
	Yes		No		t _{calc}	P
	M±SD	CI 95%	M±SD	CI 95%		
Hb (g/dL)	10.1±0.59	9.96 10.24	11.8±0.69	11.59 12.01	13.72*	< 0.001
n. erythr. (M/μl)	4.7±0.38	4.61 4.79	5.0±0.38	4.89 5.11	3.86*	< 0.001
MCV (fl)	68.9±5.22	67.65 70.15	73.7±4.14	72.46 74.94	5.11*	< 0.001
MCH (pg)	21.7±2.08	21.21 22.19	23.7±1.51	23.25 24.15	5.68*	< 0.001
MCHC (g/dL)	31.4±1.15	31.12 31.68	32.2±0.86	31.94 32.46	4.03*	< 0.001

* These parameters were analyzed in 67 anemic children and 43 non-anemic children.

Table 3 - The 25th percentile (25thP), median (Mi) and the 75th percentile (75thP) of the parameters: hematocrit (Hto), Red cell Distribution Width (RDW), serum iron and rods of anemic or non-anemic infants

Parameters	Anemia*						Mann-Whitney test	
	Yes			No			Z _{calc}	P
	25thP	Mi	75thP	25thP	Mi	75thP		
Hto (%)	31.1	32.4	33.4	35.0	36.3	38.0	8.50*	< 0.001
RDW (%)	15.3	16.4	17.5	14.4	15.6	16.8	2.52*	0.012
Serum iron (ng/dL)	28.0	35.0	45.0	34.0	53.0	72.0	4.05*	< 0.001
Ferritin [†] (ng/mL)	3.9	8.2	17.5	11.6	20.0	37.4	3.58*	< 0.001
Rods (%)	1.0	2.0	3.0	1.0	2.0	3.0	0.45	0.652

* These parameters were analyzed in 67 anemic children, and in 43 non-anemic children.

† Excluded the infants with temperature $\geq 37.5^{\circ}\text{C}$, and those with CRP ≥ 6 mg/L.

The highest negative correlations with RDW were with ferritin in infants without infection or inflammation, ($r = -0.506$), ferritin in the group as a whole ($r = -0.443$), and MCH ($r = -0.438$). These correlations are, nonetheless, weak.

Discussion

In infants aged six to twelve months in the city of São Paulo, the prevalence of anemia increased from 41.3% in 1973/74 to 53.7% in 1984/85 and 71.8% in 1995/96.^{21,26,27} In the state of São Paulo, the prevalence of anemia was 55.5% in infants from six to eight months and 62.8% in infants from nine to eleven months. These values are similar to the 60.9% obtained in the present study.²⁸

No association was observed between anemia and maternal schooling in the present study, confirming the findings of Sigulem *et al.*²¹

No association was observed in the present study between anemia in infants and per capita family income. In the city of São Paulo, no significant difference was observed between families with per capita income above and below one minimum wage in terms of anemia levels among infants under 24 months. Among those over 24 months, however, an association between income and anemia was found.²¹

Monteiro *et al* analyzed the prevalence of anemia in children between zero and 59 months in the city of São Paulo in 1995/96, finding that increased per capita income and maternal schooling are associated with reduced anemia and increased MCHC.²⁷ This analysis was not carried out separately for infants under 24 months. Nonetheless, an evaluation of the research carried out in 1984/85 and 1995/96 shows an improvement in the socioeconomic variables (per capita income and maternal schooling) and a concurrent 25% increase in anemia at all economic levels.

Table 4 - Prevalence of iron deficiency etiology in anemic infants according to the association of different criteria

Criteria	n [†]	%
Alteration of Hb + one index between MCV, or MCH, or ferritin, or serum iron	45	97.8
Alteration of Hb + one index between MCV, or MCH, or ferritin, or serum iron, or RDW	45	97.8
Alteration of Hb + RDW	41	89.1
Alteration of Hb + two indexes between MCV, or MCH or ferritin, or serum iron	40	87.0
Alteration of Hb + two indexes between MCV, or MCH, or ferritin, or serum iron, or RDW	45	97.8

* Infants with temperature < 37.5 , CRP < 6 mg/L, and presenting results for all parameters (Hb, MCV, MCH, ferritin, serum iron and RDW) were assessed.

† Number of infants that met the criteria.

Table 5 - Spearman correlation coefficient (values of r) between hematologic and biochemical variables of infants

Parameters	Hematocrit	n. of erythrocytes	MCH	MCV	Serum iron	Ferritin	Ferritin [¶]	RDW
Hemoglobin	0.946*	0.382*	0.556*	0.512*	0.467*	0.416*	0.474*	-0.313 [†]
Hematocrit		0.519*	0.401*	0.428*	0.405*	0.355*	0.388*	-0.270 [†]
n. of erythrocytes			-0.442*	-0.450*	0.044 [§]	-0.241 [‡]	-0.154 [§]	0.134 [§]
MCH				0.950*	0.424*	0.634*	0.655*	-0.438*
MCV					0.415*	0.622*	0.612*	-0.415*
Serum iron						0.292 [†]	0.350 [†]	-0.211 [‡]
Ferritin								-0.443*
Ferritin [¶]								-0.506*

* $P < 0.001$ † $P < 0.01$ ‡ $P < 0.05$ § $P > 0.05$ ¶ Excluded CRP ≥ 6 mg/L and temperature $\geq 37.5^\circ\text{C}$.

The erythrocyte count normally shows an inverse correlation with MCV, which can be confirmed in Table 5 ($r = -0.450$).⁸ This relationship was also found with MCH ($r = -0.442$) and ferritin ($r = -0.241$).

Taking hemoglobin less than 11 g/dL as the standard for diagnosis of anemia in infants, the cutoff point of MCH = 24 pg showed sensitivity of 91%, specificity of 42%, positive predictive value of 71%, negative predictive value of 75%, and accuracy of 72%.⁶ The use of the cutoff point of MCH = 22.2 pg gave greater specificity (84%) and positive predictive value (83%), but lower sensitivity (52%), negative predictive value (53%) and accuracy (64%).

The data of the present study are confirmed by Oski,¹⁴ who stated that RDW seems to be the first hematological manifestation of iron, and is more sensitive to screening for iron deficiency anemia than serum iron or serum ferritin, while also allowing the differential diagnosis of iron deficiency anemia and thalassemia. Choi and Reid state that normal RDW (RDW < 14.0) indicates normal state in healthy children.²⁹ However, only 6.0% of healthy infants researched presented with normal RDW.

Considering that the present study found only 52.2% of infants with reduced hemoglobin, MCV and ferritin, it was found that ferritin, despite being highly specific for iron deficiency, is less sensitive in infants. This confirms the affirmation of Wilson et al.,¹⁷ and contradicts the hypothesis that ferritin would be the most sensitive index of iron deficiency.^{5,10}

Among the infants with anemia and iron deficiency anemia (hemoglobin and ferritin) without infection, it was found that 41.2% and 48.3% respectively presented with hematocrit less than 32%. Allen also observed lower hematocrit alteration in anemics.³⁰ Further studies are needed to determine the hematocrit cutoff point.

Compared to Allen's study of the 18 to 36 month age range, the present study found greater correlation between hemoglobin and hematocrit ($r = 0.946$ compared to $r = 0.76$), hemoglobin and MCH ($r = 0.556$ compared to $r = 0.42$) and MCV and MCH ($r = 0.950$ compared to $r = 0.82$).³⁰ While Allen found no correlation in infants of six to twelve months between MCH and hematocrit ($r = 0.05$), hemoglobin and MCV ($r = 0.04$) and MCV and hematocrit ($r = 0.05$),³⁰ the present study found such correlations (Table 5). However, in infants from 18 to 36 months, there was greater correlation of erythrocyte numbers with hematocrit ($r = 0.57$), MCH ($r = -0.63$) and MCV ($r = -0.77$) than was found in infants. Of the variables analyzed in this study, those showing strong correlation were hemoglobin and hematocrit ($r = 0.946$) and MCV and MCH ($r = 0.950$). It was also confirmed that iron deficiency is the most common etiology for anemia in infants between six and twelve months, although prevalence levels depend on the parameters used and thus on the criteria adopted.

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