



ORIGINAL ARTICLE

Comparison between two methods of supplemental iron intake to prevent iron deficiency anemia in the first year of life of preterm infants

Gisele M.C. Vianna¹, Arthur L. Gonçalves²

Abstract

Objective: to compare 2 methods of iron supplementation (fortified formula *versus* medicinal iron drops) to prevent iron deficiency anemia in preterm infants.

Methods: sixty six premature infants weighing between 1000-2000g were included in the study. Forty infants completed the whole follow-up period, divided into 2 groups: *Group A*: 20 infants fed with iron fortified formula (11mg Fe/l); *Group B*: 20 infants fed powder cow's milk supplemented with 2mg Fe/kg/day, as drops of ferrous sulphate. At 2 and 12 months 2 mL of blood were collected to measure hemoglobin, hematocrit, serum iron, TIBC, serum ferritin and free erythrocyte porphyrins. At the 6th month 1ml of blood was drawn for hemoglobin and hematocrit determinations. Statistical analysis used the Student "t" test and (χ^2), with $P < 0.05$.

Results: there were no significant differences between the groups in terms of body weight and weight gain; hemoglobin, hematocrit, serum iron levels and TIBC saturation indexes were similar in both groups at 2 months but significantly higher in group A at 12 months of age, while free erythrocyte porphyrin levels remained stable in Group A and increased significantly in Group B ($P < 0.05$). Ferritin levels were normal in both groups at 2 month and declined sharply by 1 year of age, but only 4 (20%) infants of Group A showed levels $\leq 10\text{ng/mL}$, against 12 (60%) of the Group B ($P < 0.02$).

Conclusions: the iron fortified formula was significantly more efficient than medicinal iron drops to prevent iron deficiency anemia of preterm infants.

J Pediatr (Rio J) 2002; 78(4): 315-20: preterm infant, iron deficiency, anemia, prevention and control.

Introduction

Iron deficiency is the most common nutritional deficiency on a worldwide basis, affecting approximately one billion people, especially infants, preschool children and women, also in industrialized countries.^{1,2}

The most severe form of this disease is anemia, which arises after the depletion of iron deposits and causes reduction of physical and intellectual performance, especially in children, in which recovery is not always obtained, even after anemia is resolved.³⁻⁵

This is particularly undesirable in preterm and/or very-low-weight newborns, since they have a very low iron store at birth (restricted to that found in erythrocytes) that can be depleted extremely fast if a regular and sufficient supplementation is not received during the first month of life. This may occur because the growth rate and volemia

1. Master's Degree in Pediatrics, School of Medicine, Ribeirão Preto - Universidade de São Paulo. Assistant Professor, School of Medicine, Catanduva, SP.

2. Professor, Department of Pediatrics, School of Medicine, Universidade de São Paulo, Ribeirão Preto.

Financially supported by: CNPq, CAPES.

Manuscript received Oct 09 2001. Accepted for publication May 08 2002.

are increased and the dietary iron intake, even with breastfeeding, is not enough.⁶

Studies conducted by the World Health organization (WHO) have shown that the incidence of iron deficiency anemia in infants and children is approximately 36% worldwide, with variations from country to country or from region to region in the same country, reaching up to 12% in the most industrialized regions of the planet and up to 67% in some regions of Central Asia.² In Brazil, in surveys conducted in the state of São Paulo, from 1992 to 1994, the prevalence rates of anemia in children aged between six and 24 months were 59% and 57% respectively,^{7,8} and the number of preterm newborns affected by anemia is surely higher than this figure, with a 73.9% rate in preterm children with 12 months of life, even with regular clinical follow-up for free supplementation of medicinal iron and with the recommendation of 2mg Fe/kg/day.⁹

The most appropriate amount of iron for the prevention of late-onset anemia of prematurity is still under discussion. The American Academy of Pediatrics (AAP), by means of its Nutrition Committee (ESPGAN), and the European Society for Pediatric Gastroenterology and Nutrition recommend the supplementation of 2mg of iron/kg/day to all preterm newborns from the second month of life or after hospital discharge and until the end of the first year of life, regardless of birthweight,^{10,11} which is apparently insufficient to meet the requirements of very-low-weight newborns (VLWNB - weight < 1,500g) and of extremely premature newborns (< 1,000g), for whom doses of up to 4mg/kg/day during the whole first year of life were suggested.^{12,13} However, the daily dose is not the only factor that influences the efficiency of the treatment; the bioavailability of iron, the concomitant use of other foods and, especially, the form and the frequency at which it is administered.¹⁴

In our country, it has been shown that the fortification of milk with iron significantly reduces the rates of iron deficiency anemia in term newborns and preschool children from poor communities,¹⁵ which is not observed in preterm newborns whose mothers receive medicinal iron on a regular basis in the form of ferrous sulfate (salt with excellent bioavailability) drops for daily administration.⁹ A milk formula fortified with iron, especially developed for preterm newborns, is not available yet. This type of milk formula only exists for preterm newborns.

The present study aimed at assessing the best way to administer iron to treat its deficiency and to prevent late-onset anemia of prematurity: milk formula fortified with iron (11 mg of iron per liter) or with ferrous sulfate drops at 2mg/kg/day.

Patients and methods

Between October 1996 and November 1998, 66 preterm newborns (male and female), aged less than 36 weeks and

weighing between 1,000 and 2,000 grams, were included in the study. Forty infants were followed up during the planned period ranging from two months to 12 months. Gestational age was calculated according to the date of last menstrual cycle and by the method devised by Capurro *et al.*¹⁶ The 40 infants were classified into two groups, as described next.

Group A: 20 infants, five in each weight category, who received a milk formula fortified with 11mg of iron/liter (NAN2™) at the concentration of 13.2% (1:30).

Group B: 20 infants who received non-skimmed cow's milk powder, diluted according to age, and supplemented with ferrous sulfate drops at 2mg/kg/day, and with multivitamins.

The distribution in the groups was made by the random selection of infants in the second month of life. The 20 infants of each group were stratified into four birthweight categories (1,000g-1,250g, 1,251g-1,500g, 1,501g-1,750g and 1,751g-2,000g) as follows: for an infant weighing 1,200g, for example, the type of milk to be received was randomly selected, and the next infant in the same weight category was automatically placed in the other group. In other words, if the first infant was placed in group A, the next infant in the same weight category was placed in group B, and so on, always pairing the allocations.

Only healthy infants, living in Ribeirão Preto or in neighboring towns, who presented the following characteristics were included in the study: good postnatal outcome, absence of any chronic disease that could affect their development, infants who were not being breastfed any longer, infants whose mothers could not afford to buy milk formulas and had to rely on Health Centers in order to get cow's milk type C or whole milk powder.

Before the random selection, one of the authors (GV) informed parents about the project, the objectives of the study, the necessary exams that should be performed, occasional benefits and mutual commitment. Only infants whose parents agreed and signed a written informed consent were included in the study. The project was approved by the Ethics and Research Committee of the hospital.

The supplementation with ferrous sulfate drops was explained to each parent separately. The recommendation given was two drops/kg/day, and both the medication and the multivitamins were freely distributed to mothers of group B infants.

The formula and the milk powder were given to the mothers, and their use was strictly controlled by regular monthly visits, sometimes with no prior notice, made by a project assistant, who was in charge of collecting the empty flasks and replacing them with full ones, with a sufficient amount for the whole month, in addition to checking whether the prescriptions were being followed correctly. The iron-fortified formula was given by Nestlé, the whole milk powder was purchased in the local market with the financial support from CEPP - Centro de Estudos e Pesquisas Pediátricas (Center for Pediatric Studies and Research).

During hospital stay, the infants of both groups followed the same diet. Those who weighed more and were stronger were breastfed, while the remaining infants initially received breastmilk or human bank milk, with gradual increase of volume, according to their clinical conditions and acceptance. Newborns weighing less than 1,500g, when they reached 100ml/kg/day, were given a milk formula specific to preterm babies (PRENAN™), volume by volume, at a dilution of 16.3% (1:25) until they reached 1,800g. After that, they were given an infant formula if their mothers could not maintain lactation.

Infants were discharged from hospital when they showed regular weight gain and weighed approximately 2,000g, what occurred between the 11th and 30th day of life (means of 18 days for group A and 20 for group B) in newborns weighing more than 1,500g, and between the 23rd and 50th day of life (means of 42 and 39 days for groups A and B, respectively) in newborns weighing up to 1,500g at birth. No statistically significant difference was found between the groups ($P = 0.62$).

After hospital discharge, the weaned infants were prescribed an infant formula standardized by the hospital, at a dilution of:30 and a volume between 160-180ml/kg/day.

The preterm unit does not use erythropoietin and only performs blood transfusion on newborns outside the neonatal ICU if the newborns show a hemoglobin level below 8g/dL and/or tachycardia and insufficient weight gain. The number of transfusions with packed red blood cells did not differ significantly between the two groups during hospital stay; these transfusions were only necessary in newborns weighing less than 1,500g: four infants in group A and six in group B, with a range between one and five transfusions, and means of 1.3 and 1.4 per infant in groups A and B, respectively ($P = 0.89$).

The cow's milk powder was diluted at 10% up to the sixth month and at 15% (whole milk) after the sixth month, with the addition of 5% sucrose, according to the nutritional protocol. The formula fortified with iron was given at a concentration of 13.2% (1:30), at the volume of 160-180ml/kg/day.

The introduction of solid foods was identical for both groups, initially including crushed fruit in the third month of corrected age, which corresponds to approximately the fifth month of chronological age. Cereal porridge was introduced in minimal amounts 15 days afterwards and vegetable papa was given after the fourth month of correct age or sixth month of chronological age, depending on the weight. Meat broth was introduced in the sixth month of corrected age, and boiled and scraped egg yolk was given after 15-30 days, as proposed by Woiski.¹⁷

All 40 infants were clinically assessed by the author (G.V.) when they were 2 months \pm 3 days of life. After that, the infants were scheduled to return every month in the first six months of life and every two months from the sixth to the 12th months of life.

In the second month of life, 2 mL of blood were collected for determining the levels of hemoglobin, hematocrit, red cells, reticulocytes, serum iron, TIBC (total iron binding capacity), serum ferritin and free erythrocyte protoporphyrin (FEP). In the sixth month, 1 mL of blood was collected for the determination of the levels of hemoglobin, hematocrit, red cells and reticulocytes, and in the 12th month, the same procedure carried out in the second month was repeated.¹⁸ The quantification of hemoglobin, hematocrit, red cells and reticulocytes was made with an electronic counter (Coulter™ STKS), which was daily calibrated. The quantification of iron and TIBC was done in duplicate by the method proposed by Ramsay,¹⁹ adapted by Faggioni²⁰ for microsamples. FEP was quantified by the fluorimetric method described by Piomelli,²¹ and ferritin was quantified by a radioimmunoassay.

The minimum sample size stipulated for conclusions of the levels of hemoglobin and hematocrit, based on mean and population standard deviation of this age group, with a 90% confidence interval ($\beta = 10\%$) and significance level (α) of 5% ($P < 0.05$), was calculated in 16 infants from each group, or four infants in each weight category, by means of Student t-test, which was used to compare the means for the groups, and by the chi-square test (χ^2), used for comparing the ratios.²²

Results

To have 20 infants in each group, we had to include 35 preterm newborns in group A, and 31 in group B, with a loss of 15 and 11 infants in each group, respectively.

The reasons for these losses were the following:

– group A: eight infants changed addresses and quit follow-up, four of them did not follow the dietary recommendations properly, and three of them because the mothers administered ferrous sulfate drops, which was against the recommendation given;

– group B: nine infants for change of address and for quitting follow-up, one for receiving unprescribed whole milk and infant formulas, and one for having recurrent pneumonias.

The groups were comparable at birth, since the mean weight of infants in group A was 1,496g (\pm 73g) and 1,498g (\pm 64g) in group B; and gestational age was 32.7 (\pm 0.4) weeks and 33.1 (\pm 0.4) weeks, respectively ($P = 0.45$).

Table 1 shows the means and standard deviations from the weight means for both groups at the beginning of the assessment (two months), at six months and at 12 months, as well as the mean weight gain between the 2nd and 12th months of life (Δ 12m-2m). No statistically significant differences were observed between the two groups, which tripled their initial weight.

Table 1 - Weight (g) at 2, 6 and 12 months, (mean \pm standard errors)

Groups	n	Age (months)				Δ (12m -2m)
		2m	6m	12m		
A - Fortified formula with iron	20	2,930 \pm 117.5	6,123 \pm 195.2	8,660 \pm 238.6	5,730 \pm 200	
B - Whole milk + 2 mg of iron/kg/day	20	2,650 \pm 95.4	5,635 \pm 176.5	8,290 \pm 227.1	5,640 \pm 214	
P		0.06	0.06	0.26	0.76	

n = number of children; m = months

Table 2 shows the mean values and respective standard deviations from the means for hemoglobin and hematocrit in both groups. At the beginning (two months), no difference was found between the groups, but at six months, infants in group A, who received an iron-fortified formula, showed significantly higher means than those of group B, with increased statistical significance at 12 months.

Table 3 shows the mean serum levels (\pm standard deviation) of iron, TIBC and free erythrocyte protoporphyrin (FEP) in both groups. At two months, no statistically significant differences were found between the groups. At 12 months, the serum level of iron in infants from group B (ferrous sulfate drops) decreased while FEP increased, with statistically significant differences between the groups, whereas quickly increased in both groups, but without significant differences between them.

TIBC saturation at two months was very close in both groups (A = 30.4 \pm 2.8; B = 27.4 \pm 2.1; P = 0.40), but at 12 months, the infants who received the fortified formula presented normal saturation (23.3 \pm 1.83), which was significantly higher than that of the group which received ferrous sulfate drops (12.5 \pm 2.06), P = 0.0026.

Ferritin levels were normal at two months in both groups, 98.4 \pm 12.2 ng/mL in group A, and 161.3 \pm 39.0 ng/mL in group B (P > 0.05). The concentration decreased in both groups at 12 months, but only four infants (20%) in group A revealed ferritin levels below 10ng/mL, against 12 (60%) in group B, with a highly significant difference in the chi-square test (χ^2 = 6.66, P < 0.02).

Discussion

The study extended for more than three years due to the characteristics of the study population, to the clinical and laboratory follow-up time, and to the sample size necessary for obtaining the proposed objectives. Our study was similar to the studies conducted by other authors,^{9,24,25} which included a follow-up period of two to four months less, with consequently quicker and easier conclusions.

The number of losses²⁶ and replacements, which was apparently large, is within the scope presented in similar studies,⁹ that is, approximately 30%-40%. These losses and replacements occurred mainly because the infant's family moved to far-off towns, thus interfering with the frequency

Table 2 - Hemoglobin (g/dL) and hematocrit (%) at 2, 6 and 12 months (mean \pm standard error)

Groups	n	Age			Hb	Ht	Hb
		2 months	6 months	12 months			
A - Fortified formula with iron	20	9.1 \pm 0.29	26.6 \pm 1.01	11.2 \pm 0.16	33.2 \pm 0.48	11.6 \pm 0.16	33.1 \pm 0.45
B - Whole milk + 2 mg of iron/kg/day	20	9.3 \pm 0.25	27.3 \pm 0.72	10.1 \pm 0.25	30.0 \pm 0.66	9.8 \pm 0.36	30.6 \pm 0.89
P		0.58	0.57	0.0026	0.002	0.00001	0.01

n = number of children Hb = hemoglobin Ht = hematocrit

Table 3 - Serum iron ($\mu\text{g/dL}$), TIBC ($\mu\text{g Fe/dL}$) and free erythrocyte porphyrins – FEP ($\mu\text{g/dL}$) at 2 and 12 months (mean \pm standard error)

Age(months)	n	Serum Iron		TIBC		FEP	
		2m	12m	2m	12m	2m	12m
A - Fortified formula (NAN2™)	20	78.0 \pm 6.5	74.7 \pm 7.3	277 \pm 19	349 \pm 14	25.4 \pm 5.1	28.1 \pm 2.6
B - Whole milk + 2 mg iron/kg/day (drops)	20	73.0 \pm 7.7	47.1 \pm 4.8	275 \pm 16	385 \pm 30	21.8 \pm 4.0	53.5 \pm 10.7
P	0.62	0.002	0.92	0.28	0.93	0.02	

n = number of children m = months

of returns for assessment and supply of milk and/or medication.

Milk formulas given to infants after the second month of life did not cause them any metabolic and digestive overload or nutritional deficiencies, since the dilution and volume used did not exceed 4g of protein/kg/day, and the formulas were balanced in terms of carbohydrates and lipids, providing an adequate calorie content, and allowing infants to gain adequate weight.

The introduction of complementary (solid) foods is not in agreement with the currently used recommendation,²³ which advises introducing these foods around the sixth month of life, even in infants on artificial breastfeeding. However, as it was prescribed to both groups, it did not interfere with the results. In addition, the introduction of these foods was only one month of chronological age earlier than recommended; the mean gestational age of the two groups was approximately 33 weeks.

It is important to underscore that if breastfeeding is not possible, even for preterm infants, our state and/or towns in our region distribute cow's milk in natura or powdered, usually with no additions, but when in adequate dilution, an addition of 3 to 5% of carbohydrates, supplementation of vitamins and iron, can provide these infants with adequate development.

We opted for NAN2™ because it contains more iron (11mg Fe/l) than formulas for the first sixth months, which contain 6 to 8mg of iron/reconstituted liter; and also because it complies with the current Codex Alimentarius FAO/OMS specifications for infant formulas.

The groups, formed according to birthweight, diet, and iron supplement received during hospital stay and the number of transfusions received, were very similar and showed no significant differences, as observed in the comparison of initial levels of hemoglobin, hematocrit, serum iron, TIBC, FEP and ferritin, which did not differ significantly between groups.

Arteriography is an invasive exam and must be indicated specifically in cases of complex cardiopathy, or when there is suspicion of ring in the pulmonary artery (cases with compression of the anterior wall of the esophagus and left bronchus). In the remaining situations, arteriography can be avoided, since the precise definition of the malformation is only established on the surgical act itself and, as already mentioned, in several situations, the structures of the vascular ring are atresic and are not contrasted in the arteriography.

By analyzing the different indices over which the influence of increased volemia and dilution was similar in both groups, with tripled weight in relation to the first two months (Table 1), we could see that infants in group A showed hemoglobin and hematocrit levels significantly higher than those of group B at six months, with an increase at 12 months. These results show that the formula fortified with iron was more efficient in preventing late-onset anemia of prematurity than the daily administration of 2mg of ferrous sulfate drops/kg.

At 12 months, the serum iron levels were significantly higher than those of infants in group A, which contributed to TIBC saturation levels way above the minimum amount tolerated for age (12%), whereas 50% of those infants who received ferrous sulfate drops (group B) presented a saturation that was less than or equal to 12%, showing a better nutritional status in terms of iron in group A.

At 12 months, infants in group B showed significantly higher levels of FEP than their own levels at two months and in relation to infants in group A, which clearly indicates iron deficiency for the synthesis of hemoglobin at this age, confirmed by low levels of hematocrit and hemoglobin in infants of this group. Iron stores, assessed by ferritin, showed to be depleted ($< 10\text{mg/mL}$) at 12 months, in most infants of group B, thus confirming the higher efficiency of iron supplementation in fortified formulas.

One could question whether the dose of 2mg/kg/day is insufficient for very-low-weight preterm newborns ($< 1,500\text{g}$) and whether this could have ethical implications.

However, despite the recommendations made by experts^{12,13} that the supplementation for very-low-weight preterm newborns should be greater than 2-4mg/kg/day, the Nutrition Committee of the AAP and ESPGAN^{10,11,26} have not changed their recommendation of 2mg/kg/day, certainly because they do not have definitive studies about it. On top of that, the efficiency of infant formulas fortified with 6, 9, 11 or 12mg of iron/liter²⁴⁻²⁶ has been increasingly recognized, since they offer quite less than 2mg of iron/kg/day for the prevention of iron deficiency and of late-onset anemia of prematurity, even for very-low-weight newborns.

Therefore, the present study, despite the limitations of long-term clinical assays and the difficulty in rigidly controlling all the variables involved in the assessment, showed that iron supplementation to preterm newborns by means of infant formulas fortified with 11mg of iron per liter was incontestably more efficient than the supplementation by means of ferrous sulfate drops in a single dose of 2mg/kg/day. An explanation to this could be that the regular and fragmented intake of this nutrient at different times of the day enhances iron absorption.

By considering our results, the results obtained through recent studies,^{24,25} the evidence of safety and good tolerability of formulas fortified with up to 15mg of iron/liter²⁵ and the efficiency of daily ferrous sulfate drops,⁹ preterm newborns should be given infant formulas fortified with iron instead of cow's milk in natura or nonfortified milk powder, if breastfeeding is not possible. Ferrous sulfate drops should be given to infants on natural breastfeeding because, in spite of the good bioavailability of iron in human milk, its amount is not sufficient, even for full-term newborns who are exclusively breastfed.^{6,27}

References

- United Nations, Administrative Committee on Coordination – Subcommittee on Nutrition. Second Report on the World Nutrition Situation. World Health Organ Tech Rep Ser; 1992.p.40-8.
- Lönnerdal B, Dewey KG. Epidemiologia da deficiência de ferro no lactente e na criança. *Anais Nestlé* 1996;52:11-19.
- Walter T, De Andraca I, Chadud P, Perales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics* 1989;84:7-17.
- Lozoff B, Jimenez E, Wolf A. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med* 1992;326:575-6.
- Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000;105:1-11.
- Siimes MA, Salmenperä L, Perheentupa J. Exclusive breast-feeding for 9 months: risk of iron deficiency. *J Pediatr* 1984;104:196-9.
- Torres MAA, Sato K, Souza Queiroz S. Anemia em crianças menores de 2 anos atendidas nas Unidades Básicas de Saúde no Estado de São Paulo. *Rev Saúde Públ* 1994;4:290-4.
- Torres MAA, Sato K, Lobo NF, Souza Queiroz S. Efeito do uso de leite fortificado com ferro e vitamina C nos níveis de hemoglobina e condição nutricional de crianças menores de 2 anos. *Rev Saúde Públ* 1995;4:301-7.
- Borigato EV, Martinez FE. Iron nutritional status in Brazilian preterm infants fed food cooked in iron pots. *J Nutr* 1998;128: 855-9.
- American Academy of Pediatrics Committee on Nutrition. Nutritional needs of low-birth-weight infants. *Pediatrics* 1985;75:976-86.
- European Society of Pediatric Gastroenterology and Nutrition. Nutrition and feeding of preterm infants. *Acta Paediatr Scand* 1987;336 (Supl):1-14.
- Oski FA. Iron deficiency in infancy and childhood. *N Eng J Med* 1993;329:190-3.
- Siimes MA, Järvenpää AL. Prevention of anemia and iron deficiency in very-low-birth-weight infants. *J Pediatr* 1982;101:277-80.
- Fomon SJ, Nelson SE, Ziegler EE. Retention of iron by infants. *Annu Rev Nutr* 2000;20:273-90.
- Torres MAA, Lobo NF, Sato K, Souza Queiroz S. Fortificação do leite fluido na prevenção e tratamento da anemia carencial ferropriva em crianças menores de 04 anos. *Rev Saúde Públ* 1996;30: 350-7.
- Capurro H, Konichesky S, Fonseca D, Caldeyro-Barcia RA. Simplified method for diagnosis of gestational age in the newborn infant. *J Pediatr* 1978;93:120-4.
- Woiski JR. Alimentação do lactente. In: Woiski JR, editores. *Nutrição e dietética em pediatria*. 4th ed. São Paulo: Atheneu; 1995. p.109-26.
- Dallman PR. Diagnóstico laboratorial da deficiência de ferro no lactente e na criança pequena. *Anais Nestlé* 1995;52:18-24.
- Ramsay WNM. The determination of iron in blood plasma or serum. *Clin Chim Acta* 1957;12:214-20.
- Faggioni LG. Contribuição para o estudo do metabolismo de ferro em crianças desnutridas [tese]. Ribeirão Preto: Universidade de São Paulo; 1969.
- Piomelli S. A micromethod for free erythrocyte porphyrins: the FEP test. *J Lab Clin Med* 1973;81:932-40.
- Berquó E. *Bioestatística*. 1st ed. EDUSP: São Paulo; 1969.
- Giugliani ERJ, Victora CG. Alimentação complementar. *J Pediatr (Rio J)* 2000;76(Supl 3):S253-62.
- Griffin IJ, Cooke RJ, Reid MM, Mc Cormick KPB, Smith JS. Iron nutritional status in preterm infants fed formulas fortified with iron. *Arch Dis Child Fetal Neonatal Ed* 1999;81:45-9.
- Franz AR, Mihatsch WA, Sander S, Kron M, Pohlandt F. Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams. *Pediatrics* 2000;106:700-6.
- American Academy of Pediatrics. Committee on Nutrition. Iron fortification of infant formulas. *Pediatrics* 1999;104:119-23.
- Pisacane A, De Vizia B, Valiante A. Iron status in breast-fed infants. *J Pediatr* 1995;127:429-31.

Correspondence:

Dra. Gisele Maria Couto Vianna
Rua Aracaju, 821 - Centro
CEP 15801-150 – Catanduva, SP, Brazil
Phone: +55 17 522.6322 / Fax: +55 17 522.0550
E-mail: giselemari@zup.com.br