

Recommendation and use of ferrous sulphate in 12- and 24-month-old children: evaluation in the 2015 Pelotas Birth Cohort

Recomendação e uso de sulfato ferroso em crianças de 12 e 24 meses de idade: avaliação da coorte de nascimentos de Pelotas, RS, de 2015

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ABSTRACT: *Aim:* To verify the prevalence of recommendation of iron supplementation among children aged 12 and 24 months. *Methodology:* All children born in the maternities of Pelotas/RS in 2015 were eligible for the Cohort. The outcomes were the recommendation of ferrous sulphate by health professionals and its use. *Results:* The cohort followed up 4,275 children. Approximately 64.0% of them were recommended to receive iron supplementation until 12 months of age. Among these, 68.8% used iron. From 12 to 24 months, 39.4% of the children received a prescription of iron supplementation, and among them, 26.2% actually used it. At 12 months, after adjusted analysis, higher maternal education, higher family income, lower parity, and low birth weight remained associated with the outcome. At 24 months, after adjusted analysis, we observed a higher recommendation of iron supplementation among mother with lower parity and for children with low birth weight. *Conclusion:* There was a low frequency of recommendation and low rate of use of iron among children. These findings are highly relevant given the high prevalence of anemia observed in children this year. The low recommendation of iron use among children up to 24 months of age, and the low use among those who are recommended to use it reflect the need for coordinated actions among health professionals and the expansion of knowledge among mothers to enable a wider reach of this important public policy.

Keywords: Longitudinal studies. Child. Vitamins. Iron salts. Program evaluation.

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RESUMO: *Objetivo:* Verificar a prevalência e os fatores associados à recomendação de uso de ferro a crianças aos 12 e aos 24 meses de idade. *Metodologia:* Todas as crianças nascidas nas maternidades de Pelotas em 2015 foram elegíveis para a coorte. Os desfechos foram a recomendação de uso de sulfato ferroso por profissional de saúde e a respectiva utilização. *Resultados:* A coorte acompanhou 4.275 crianças. Aproximadamente 65% receberam recomendação de suplementação de ferro até 12 meses. Destas, 68,8% fizeram a utilização recomendada. Dos 12 aos 24 meses, 39,4% das crianças receberam recomendação de suplementação de ferro e 26,2% fizeram o uso recomendado. Aos 12 meses, após ajuste, permaneceram associadas com recomendação de uso de ferro: maior escolaridade, maior renda, menor paridade e baixo peso ao nascer. Aos 24 meses, após ajuste, observou-se maior recomendação às mães com menor paridade e às crianças com baixo peso ao nascer. *Conclusão:* Houve baixa recomendação e baixa utilização de ferro. Esses achados são preocupantes diante da alta prevalência de anemia em crianças na faixa etária estudada. A baixa recomendação de profilaxia de ferro a crianças até 24 meses de idade, assim como a baixa utilização entre aquelas que receberam a orientação de uso refletem a necessidade de ações coordenadas entre profissionais de saúde e de ampliação do conhecimento entre as mães para possibilitar maior alcance dessa importante política pública.

Palavras-chave: Estudos longitudinais. Criança. Vitaminas. Sais de ferro. Avaliação de Programas e projetos de saúde.

INTRODUCTION

Iron deficiency anemia (IDA) is one of the main consequences of nutritional deficiency and, due to its high worldwide prevalence, it is considered a public health problem^{1,2}. IDA affects all social strata, and may be higher in populations in greater social vulnerability, affecting mainly pregnant women and children under two years of age².

Among the factors that can contribute to the onset of anemia, the main one is the need for increased iron intake due to the child's peak growth period, which is associated with low-mineral diets, especially high availability iron³⁻⁶. In addition to these factors, the following stand out: parasitic infections, chronic inflammation, genetic diseases and nutrient deficiencies (folate, vitamin B12 or vitamin A)⁷.

A systematic review carried out with data from 1995 to 2011, with a worldwide representative estimate of 107 countries, showed that the prevalence of anemia among children under five years of age was around 43.0% (95%CI 38.0; 47.0)⁸. In Brazil, population-based studies have reported from 20.9 to 54.0%^{1,9,10}, depending on the region of the country, always being higher in populations in evident conditions of social inequity.

Children who had anemia in the first two years of life, even if treated, have a lower immune response, which favors the occurrence or worsening of infectious diseases^{2,11} and leads to a greater probability of cognitive development deficit¹¹, which may impact school performance in children. later ages, even in low productivity as adults, which impacts negatively in human capital in adult life^{11,12}.

Considering the importance of preventing IDA, the Ministry of Health, through the National Iron Supplementation Program (PNSF, in the Portuguese acronym)¹³, has recommended since 2005 the prophylactic supplementation of ferrous sulphate for children from six to 24 months of age, and under six months of age when the child was born prematurely or underweight. The PNSF recommends daily administration of iron until the child is 24 months old, and it is available for free to users of the Brazilian Unified Health System (SUS) in Basic Health Units¹⁴.

This study aimed to:

- identify the prevalence of recommendation of ferrous sulphate to children at 12 and 24 months of age, based on the 2015 birth cohort in Pelotas, RS, which was carried out by physicians or other health professionals, according to the PNSF;
- evaluate the use of iron by children aged 12 and 24 months who received a prescription for the use of ferrous sulphate;
- verify the factors associated with the recommendations of prophylaxis with iron salts in these children.

METHODOLOGY

The city of Pelotas is located in the south of Brazil and its current population is approximately 300 thousand inhabitants. In the 1980s, the first cohort study began, in which children born in maternity hospitals and whose mothers lived in the urban area were eligible to participate. It was subsequently also carried out in 1993, 2004 and 2015, being known worldwide as the birth cohorts of Pelotas¹⁵. In such studies, several aspects of maternal and child health were addressed, including the use of medications.

All children born in the maternity hospitals of Pelotas, between January 1 and December 31 of 2015, whose mothers lived in the urban area of the municipality or in Jardim América, were eligible for the study. The interviews of the perinatal study took place in the hospital, at the time of birth, and the other follow-ups took place at home at three and 12 months, and mostly at the clinic located at the Epidemiological Research Center of the Federal University of Pelotas at 24 months¹⁵.

The study outcomes were the recommendation for the use of ferrous sulphate by a health professional and its use by children who were recommended to, focusing on the evaluation of the policy that recommends prophylactic use of iron salts from six to 24 months of age¹³. Information about the use of iron salts was obtained by the following questions: at 12 months of age, “Did any doctor or health professional indicate iron, ferrous sulphate or anemia medicine for <CHILD> from the sixth month until now?” and, at 24 months, “Did any doctor or health care professional recommend iron, ferrous sulphate or anemia medicine to <CHILD> after he/she turned one year old?”. For the outcome of iron use, the questions were: “How long did <CHILD> use this medicine after six months of age?” and “How long did <CHILD> use this medicine after one year of age?”, at 12 and 24 months, respectively.

The independent variables were collected in the perinatal study and were categorized for purposes of analysis in this study. Variables referring to demographic, socioeconomic aspects, parity, low birth weight and prematurity were used as follows: gender of the child (male/female), maternal skin color (white, black and mixed race/other), maternal schooling in complete years of study (0–4, 5–8, 9–11 and 12 years or more), family income in Reais (later categorized into quintiles – 1st poorest quintile and 5th richest quintile) and parity (1, 2, 3 and 4 or more children). Full gestational age at delivery was calculated according to the date of the last menstrual period (LMP) and ultrasound images (<37 weeks: premature and ≥ 37 weeks: term)¹⁵, birth weight was measured in grams (<2,500g considered low weight).

The analyses were performed using the Stata 15.0 software. The description of the sample of mothers and children was made in relation to the independent variables, and the prevalence of the outcome recommendations for the use of iron at 12 and 24 months and its use by the children were calculated in relation to these variables. The factors associated with iron recommendation were analyzed by Poisson regression with robust variance¹⁶, obtaining prevalence ratios (PR), respective 95% confidence intervals (95%CI) and p values. Based on this regression, Wald tests were used for heterogeneity and linear tendency for ordinal categorical variables. For adjusted analysis, only variables with $p < 0.20$ were considered. Associations with p less than 0.05 were considered statistically significant.

The 2015 birth cohort project was submitted to and approved by the Research Ethics Committee of the School of Physical Education of *Universidade Federal de Pelotas*, under protocol number 26746414.5.0000.5313. All participating mothers signed an informed consent form (IC) agreeing to participate in the study.

RESULTS

The sample of the 2015 birth cohort of Pelotas was composed of 4,275 live births. At 12 months, mothers or guardians of 4,018 children (95.4%) were interviewed, and at 24 months, interviews were conducted with 4,014 children (95.4%).

Table 1 shows the characteristics of the sample according to variables. Just over half of the children were males (50.6%). Most were born weighing $\geq 2,500$ g (89.9%) and 84.5% were considered at term (≥ 37 weeks of gestation). As for the characteristics of mothers, 70.8% were white, 34.1% had between 9 and 11 years of study, and 49.4% were primiparous. The average monthly family income in the poorest quintile (1st quintile) was approximately R\$ 728 and in the richest quintile (5th quintile) R\$ 8,586.

The graphs in Figure 1 show the percentage of recommended prophylactic iron supplementation and its use at 12 months and 24 months of age. Approximately 65% (95%CI 62.4; 65.3) of the children in the 2015 cohort were recommended to use iron supplementation from 6 to 12 months of age. Among these, only 68.8% (95%CI 67.0; 70.6) adhered to the use of ferrous sulphate. From 12 to 24 months of age, only 39.4% (95%CI 37.8; 40.9) of the children received a prescription for prophylactic iron supplementation, and among these, 26.2% (95%CI 24.1; 28.4) adhered to use.

Table 1. Characteristics of mothers and children in the 2015 birth cohort of Pelotas (n = 4,275).

	Sample		95%CI
	N	%	
Child's sex			
Male	2,158	50.6	49.1; 52.1
Female	2,106	49.4	47.8; 50.8
Low birth weight			
No	3,830	89.9	89.0; 90.8
Yes	428	10.1	9.1; 11.0
Preterm (<37 weeks)			
No	3,612	84.5	83.4; 85.5
Yes	663	15.5	14.4; 16.6
Mother's skin color			
White	3,024	70.8	69.4; 72.2
Black	667	15.6	14.5; 16.7
Brown/other	577	13.6	12.5; 14.6
Mother's schooling			
0–4	391	9.2	8.3; 10.1
5–8	1,095	25.6	24.4; 26.9
9–11	1,458	34.1	32.7; 35.5
12 or more	1,330	31.1	29.7; 32.5
Family income in quintiles			
Q1 (poorer)	796	19.8	18.6; 21.0
Q2	807	20.1	18.8; 21.3
Q3	804	20.0	18.8; 21.2
Q4	895	22.3	21.0; 23.6
Q5 (richer)	714	17.7	16.6; 18.9
Parity			
1	2,112	49.4	47.9; 50.9
2	1,321	30.9	29.5; 32.3
3	472	11.1	10.1; 12.0
4 or more	368	8.6	7.8; 9.4

95%CI: 95% confidence interval.

Tables 2 and 3 show the prevalence of recommendation for prophylactic iron supplementation by a physician or other health professional at 12 and 24 months and the crude and adjusted analysis between the recommendation and independent variables. At 12 months, after adjusted analysis, mothers' higher education level — 12 years or more of study remained associated with the outcome [PR = 1.25 (95%CI 1.10; 1.43)], higher family income — 5th quintile [PR = 1.17 (95%CI 1.07; 1.28)], lower parity — primiparous [PR = 1.44 (95%CI 1.25; 1.64)] and low birth weight [PR = 1.14 (95%CI 1.05; 1.24)] (Table 2). At 24 months, after adjusted analysis, a higher recommendation for iron supplementation was observed among primiparous women [PR = 1.35 (95%CI 1.12; 1.61)] and also among children with low birth weight [(PR = 1.21 (95%CI 1.10; 1.40)] (Table 3).

In the 12-month follow-up, 794 children were not receiving iron supplementation after six months of age. Most mothers (70.0%) reported that they did not take iron supplementation due to lack of medical recommendation, 13.0% said they did not think it was necessary, 4.0% reported the appearance of adverse reactions in children and only 1.0% reported

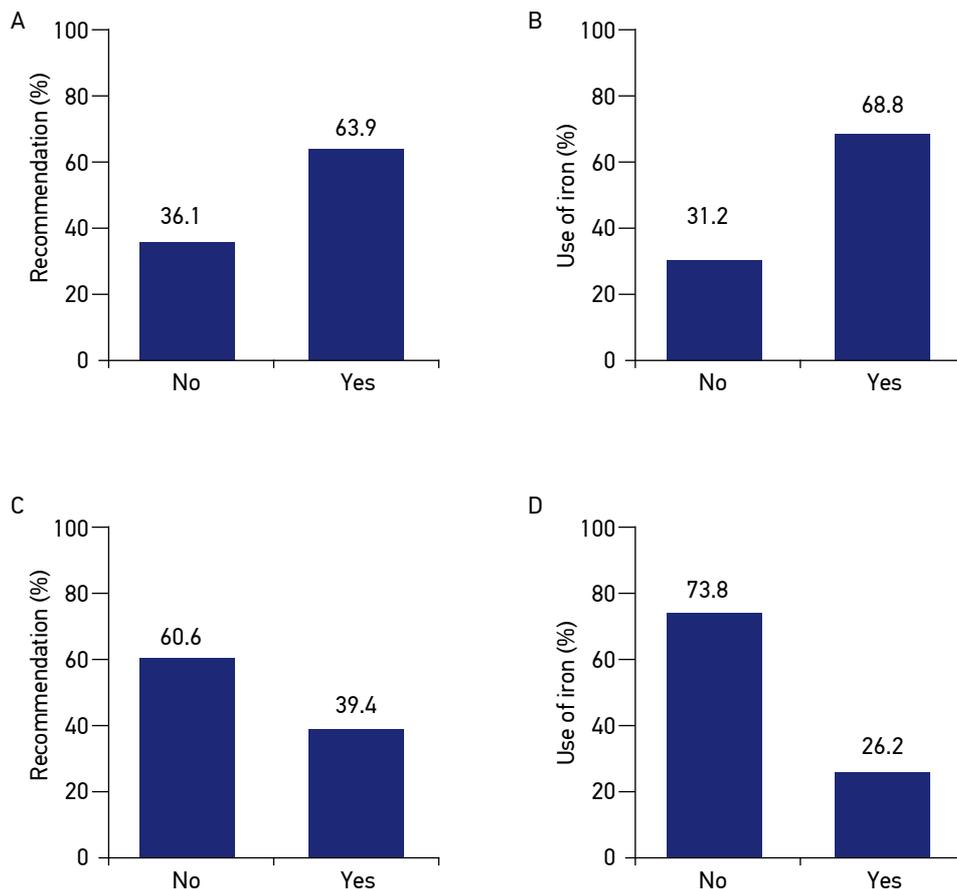


Figure 1. Recommendation for prophylactic iron supplementation and use among children who received guidance on iron use. Monitoring at (A, B) 12 months of age and (C, D) 24 months of age, 2015 birth cohort of Pelotas.

Table 2. Prevalence of recommendation for prophylactic iron supplementation by a health professional during the 12-month follow-up of the 2015 birth cohort of Pelotas, RS, Brazil, 2015.

	Gross analysis				Adjusted analysis		
	P	PR	95%CI	p	PR	95%CI	p
Child's sex							
Male	65.0	1		0.142	1		0.181
Female	62.8	0.96	0.92 – 1.0		0.97	0.92 – 1.01	
Low birth weight							
No	62.9	1		< 0.001	1		0.002
Yes	73.8	1.17	1.10 – 1.3		1.14	1.05 – 1.24	
Preterm ^b							
No	62.9	1		< 0.001	1		0.361
Yes	69.6	1.11	1.0 – 1.20		1.04	0.96 – 1.11	
Mother's skin color							
White	66.9	1.16	1.08 – 1.26	< 0.001	1.04	0.96 – 1.12	0.082
Black	56.0	1.01	0.88 – 1.08		0.95	0.86 – 1.05	
Brown/other	57.4	1			1		
Mother's schooling							
0–4	46.2	1		< 0.001	1		< 0.001 ^a
5–8	55.4	1.2	1.10 – 1.36		1.05	0.92 – 1.19	
9–11	65.1	1.41	1.25 – 1.58		1.18	1.04 – 1.34	
12 or more	74.6	1.61	1.43 – 1.81		1.25	1.10 – 1.43	
Family income ^c quintiles							
Q1 (poorer)	54.6	1		< 0.001	1		0.001 ^a
Q2	58.9	1.1	1.0 – 1.17		1.04	0.94 – 1.13	
Q3	64.3	1.18	1.08 – 1.28		1.09	0.99 – 1.18	
Q4	66.3	1.21	1.12 – 1.31		1.06	0.97 – 1.16	
Q5 (richer)	77.4	1.41	1.31 – 1.53		1.17	1.07 – 1.28	
Parity							
1	69.2	1.58	1.40 – 1.79	< 0.001	1.44	1.25 – 1.64	< 0.001 ^a
2	63.2	1.44	1.27 – 1.64		1.34	1.16 – 1.52	
3	57.4	1.31	1.13 – 1.52		1.27	1.08 – 1.46	
4 or more	43.6	1			1		

^ap linear trend; ^b<37 weeks; ^cin Reais, presented in quintiles; P: prevalence; PR: prevalence ratio; 95%CI: 95% confidence interval.

Table 3. Prevalence of recommendation for prophylactic iron supplementation by a health professional during the 24-month follow-up of the 2015 birth cohort of Pelotas. Pelotas, RS, Brazil, 2015.

	Gross analysis				Adjusted analysis		
	P	PR	95%CI	p	PR	95%CI	p
Sex							
Male	40.8	1		0.064	1		0.071
Female	37.9	0.93	0.86 – 1.0		0.93	0.86 – 1.0	
Low weight^b weight							
No	38.4	1		< 0.001	1		0.006
Yes	49.0	1.27	1.14 – 1.42		1.21	1.10 – 1.40	
Preterm^c							
No	38.1	1		< 0.001	1		0.099
Yes	46.8	1.23	1.11 – 1.35		1.11	0.98 – 1.25	
Skin color^d							
White	38.3	0.94	0.84 – 1.05	0.057	0.93	0.81 – 1.03	0.08
Black	43.2	1.06	0.92 – 1.21		1.05	0.90 – 1.19	
Brown/other	40.6	1			1		
Schooling^d							
0–4	38.6	1		0.538			
5–8	37.7	0.98	0.84 – 1.14				
9–11	40.7	1.05	0.91 – 1.21				
12 or more	39.5	1.03	0.88 – 1.18				
Family income^c quintiles							
Q1 (poorer)	39.7	1		0.080	1		0.516
Q2	37.8	0.95	0.84 – 1.08		0.98	0.84 – 1.08	
Q3	42.2	1.06	0.94 – 1.20		1.07	0.92 – 1.18	
Q4	41.5	1.04	0.92 – 1.17		1.05	0.89 – 1.16	
Q5 (richer)	35.8	0.90	0.78 – 1.03		0.90	0.78 – 1.04	
Parity^d							
1	40.8	1.29	1.10 – 1.53	0.024	1.36	1.12 – 1.61	0.002 ^a
2	39.3	1.25	1.05 – 1.48		1.30	1.05 – 1.52	
3	39.4	1.25	1.03 – 1.52		1.33	1.06 – 1.59	
4 or more	31.4	1			1		

^ap linear trend; ^blow birth weight; ^c<37 weeks; ^dMothers' variables ^ein Reais, presented in quintiles; P: prevalence; PR: prevalence ratio; 95%CI: 95% confidence interval.

having difficulty to obtain the supplement in the public network. Other reasons not specified totaled 12.0% (data not shown).

DISCUSSION

Although IDA is considered one of the greatest nutritional problems in the world, affecting 40% of children up to 2 years of age², there are few studies in the Brazilian literature investigating the recommendation for ferrous sulphate supplementation and its use by children. This study evaluated the recommendation of ferrous sulphate as prophylaxis of IDA in children from six to 24 months of age, according to the national regulations in force¹⁴, as well as adherence to this use. The prevalence of ferrous sulphate prophylactic recommendation was higher at 12 months of age (63.9%) compared to 24 months (39.4%), which also occurred in relation to the use of iron supplementation, being 39.4 and 26.2%, respectively.

One can observe that the older the child, the lower the prevalence of recommendation, since in this study that recommendation dropped to almost half from 12 to 24 months, and the use also decreased significantly during this period. The recommendation of iron for children aged 6 to 24 months by physicians or other health professionals far below expectations is worrisome. Health professionals are responsible for recommending prophylactic iron supplementation to prevent anemia, considering that supplementation is a universal policy that must be followed, according to the World Health Organization (WHO), the Ministry of Health, and the Brazilian Society of Pediatrics^{13,17-19}.

As to any type of pharmacological treatment, a systematic review with data published over a period of 50 years reported an average rate of around 25% of individuals who did not adhere to respective treatment²⁰. According to the WHO, non-adherence to pharmacological treatments for longer periods in the general population is around 50%^{21,22}. In our study, a higher prevalence of non-use was observed, and several factors may have contributed to this situation. It should be noted that in the case of therapeutic management in children, the main facilitator is the mother. In a population-based, prospective study on anemia prevention using ferrous sulphate, conducted in Viçosa (MG), in 2013 by Azeredo et al., 56.7% of children adhered to the recommendation of supplementation and this rate was lower among mothers who did not have other preventive attitudes, such as better eating habits and offer of iron-source foods²³.

In the same study, the authors found that all mothers had difficulties in administering the medication to their children, but such difficulties were overcome by the mothers who adhered to the treatment. Forgetfulness was also reported by both groups of mothers; however, among those with low adherence, the “forgetting” time was longer: more than seven days²³.

Adherence to a specific treatment, according to the WHO, has five dimensions that are interrelated: the disease, the treatment, the socioeconomic conditions, the system (health team), and the patient²¹. Thus, the use of a medication is directly related to adherence to

treatment, and the fact that “adherence” is related to prophylaxis, that is, the treatment is in apparently healthy individuals, can cause mothers to lack motivation to start or even continue the treatment²³.

The importance of a health professional’s guidance and advice is highlighted here, and it can reflect both positively and negatively on the treatment of a patient. A cross-sectional study, carried out with children aged 12 to 24 months, diagnosed with IDA, found that families that received information about anemia, including consequences, severity and importance of prevention, were the ones with the highest adherence rates²⁴.

Adequate orientation of patients regarding possible adverse effects and the duration of treatment is essential for therapeutic success²⁵. A difficulty commonly presented in studies evaluating the use of ferrous sulphate and adherence to its supplementation is the presence of adverse reactions; mothers who had low adherence reported a much higher prevalence of reactions than those with high adherence (43.6 versus 19.6%, respectively)^{23,25}. In addition, it should be noted that adherence to the use of medications for continuous use decreases with time, regardless of treatment²⁶. In this sense, daily use of prophylactic ferrous sulphate supplementation for two years contributes to decreased adherence²¹, as observed in the present study.

As for the factors associated with the recommendation of iron supplementation by a health professional, it was observed that, at 12 months of age, there was a higher recommendation for use by children whose mothers had higher education, higher income and fewer children, as well as low birth weight children. Perhaps this is because mothers with more schooling in general have the highest income and have more knowledge, which makes them carry out a greater number of consultations, most likely in the private health network. At the age of 24 months, children of primiparous women and children with low birth weight remained associated with recommendation of ferrous sulphate supplementation.

The recommendation by the Ministry of Health¹⁴ is that every preterm or newborn with low weight, even on exclusive breastfeeding, receive iron supplementation from the 30th day after birth and not only at six months of age. Low birth weight or premature children have lower iron stores and a higher rate of postnatal growth, important factors that increase their susceptibility to iron deficiency anemia²⁷. Mothers of low weight or premature newborns may also be more careful and regular in childcare follow-ups, often being followed up in specialized outpatient clinics. The differentiated attention given to these children due to problems associated with low weight, as well as the special recommendation by the ministry of health, may have contributed to the greater care of professionals regarding the prescription of iron for this group.

This study had as limitations the use of self-report to measure the recommendation of prophylaxis performed by a physician or other health professional and the measure its use as prophylaxis. In this sense, there is the possibility of mothers’ recall bias, considering that there is usually a greater tendency to remember when there is exposure to some specific condition, and in this study, as the preventive measure was carried out, mothers may have

forgotten the recommendation given at 6-12 months of the child, so the results found may have been overestimated.

The lack of information about health services (both public and private) and the number and frequency of childcare consultations may also have limited the understanding of results, as these are factors that can influence the receipt and reinforcement of recommendations on the use of iron salts. Another possible limitation could be the memory bias among mothers who had premature children with low birth weight, as they tend to remember more of all the care and recommendations given by health professionals, which contributes very positively to adherence to treatment.

The fact that this is the first population-based study that assessed the prevalence of recommendation of IDA prophylaxis by a physician or other health professional and associated factors is one of the strengths of this study. In addition, the low percentage of losses to follow-up stands out: around 5% in both follow-ups, at 12 and 24 months.

Despite the important measures already adopted to prevent anemia in children, these results indicate a low recommendation for the use of ferrous sulphate by physicians and/or other health professionals, in addition to low use among children who have received the prescription of use. These findings are considered highly relevant in view of the high prevalence of IDA observed in children up to two years of age. More efforts are needed to increase the effectiveness of the actions already implemented. One of these actions must be within the scope of primary health care, which can join efforts aiming at the highest recommendation for the use of iron and reinforcing its importance, as well as promoting the expansion of knowledge through educational actions aimed at mothers to enable greater treatment follow-up.

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