ARCHIVOS LATINOAMERICANOS DE NUTRICION
Organo Oficial de la Sociedad Latinoamericana de Nutrición Suplemento Vol. 51 N° 1, 2001

Relative effectiveness of iron bis-glycinate chelate (Ferrochel) and ferrous sulfate in the control of iron deficiency in pregnant women

Sophia Cornbluth Szarfarc, Luz Marina Núñez de Cassana, Elizabeth Fujimori, Elvira Maria Guerra-Shinohara, Ida Maria Vianna de Oliveira

Sao Paulo University. Sao Paulo - Brazil, National University of Cajamarca , Perú

SUMMARY. The relative effectiveness of daily supplementation of iron deficiency during pregnancy using 15 mg/day of iron from iron-bis-glycinate chelate (71 pregnant women), or 40 mg iron from ferrous sulfate (74 pregnant women) was evaluated by measuring hemoglobin, transferrin saturation and serum ferritin, at the beginning of the study (<20 weeks of pregnancy) and at 20-30 weeks and 30-40 weeks thereafter. Ingestion for 13 weeks or more was considered adequate. Seventy three percent of the Ferrochel consuming group and 35% of the ferrous sulfate consuming group were considered to have taken the treatment adequately. The decrease in levels of all the measured parameters was significantly less pronounced in the group that consumed Ferrochel in spite of the lower treatment dose. Iron depletion was found in 30.8% of the women treated with Ferrochel and in 54.5% of the women than consumed ferrous sulfate. Of the factors responsible for non compliance taste was reported in 29.8% of the ferrous sulfate consumers and none in the groups that consumed Ferrochel. It is concluded that daily supplementation with Ferrochel was significantly more effective, in spite of the lower dose, than supplementation with ferrous sulfate.

Key words:Ferrochel, iron supplementation, iron deficiency anemia, iron deficiency, pregnancy, Ferrochel's tolerance, Ferrochel effectiveness.

RESUMEN. Efectividad relativa del hierro bis-glicinato quelado (Ferrochel) y del sulfato ferroso en el control de la deficiencia de hierro en mujeres embarazadas. La efectividad relativa de la suplementación diaria con sulfato ferroso (FeSO4) o con hierro aminoquelado (Ferrochel, FeAAC) se estudió en 145 mujeres de menos de 20 semanas de embarazo distribuidas en dos grupos. Un grupo (71 mujeres) fue suplementado con 15 mg de hierro por día provenientes de Ferrochel, y el otro (74 mujeres) con 40 mg de hierro por día provenientes de sulfato ferroso. Se efectuaron mediciones de hemoglobina, ferritina y saturación de trasferrina al ingreso al programa (<20 semanas de embarazo), entre 20-30 semanas y entre 30-40 semanas. La ingesta ininterrumpida por 13 semanas o más se consideró adecuada. La disminución en los valores de todos los parámetros medidos fue menor en el grupo tratado con Ferrochel, a pesar de que la dosis fue mas pequeña. Depauperación de hierro se encontró en 30.8% de las mujeres tratadas con Ferrochel y en 54.5% de aquellas tratadas con sulfato ferroso. Entre los factores informados como responsables del abandono del tratamiento se encontró que el sabor fue el factor mas importante para las consumidoras de sulfato. Sabor indeseable no fue informado por las mujeres que consumieron Ferrochel. Se concluye que la suplementación diaria con Ferrochel fue sifnificativamente mas efectiva a pesar que la dosis usada fue menor que la dosis de sulfato ferroso.

Palabras clave: Ferrochel, suplementación con hierro, anemia ferropriva, deficiencia de hierro, embarazo, tolerancia a Ferrochel, efectividad del Ferrochel.

INTRODUCTION

Pregnant women constitute the most vulnerable group for iron deficiency. According to WHO estimates (1), in developing countries 56% of pregnant women suffer from iron deficiency anemia, which indicates that a much higher proportion may be iron deficient.

Iron deficiency anemia affects the fetus and the pregnant mother leading to impairment in oxygen supply to the fetus favoring the development of fetal hypoxia which has been associated with prematurity, low birth weight and neonatal and perinatal death (2-5).

The increased need of iron during pregnancy, specially after the second trimester, makes iron supplementation mandatory (6). In many countries, including Brazil, mandatory supplementation programs have been established to control the development of iron deficiency during pregnancy (7). Following WHO suggestions (8), the iron compound more frequently used is ferrous sulfate due to its low cost and reasonable availability (9,10).

In spite of its efficiency from a hematological point of view, ferrous sulfate supplementation shows low efficacy for the control of iron deficiency anemia (11,12), due to poor compliance with the treatment because of its disagreable

flavor and collateral effects such as nausea, vomit, constipation, diarrhea, abdominal pain.

Besides the above problems, usually there are also administrative problems such as deficient coverage in the health services, lack of compliance and logistiç problems in the supplement distribution (6). It has to be stressed, that iron deficiency anemia does not present specific signs or symptoms. This associated with the lack of knowledge of the general population on the importance of the disease for the health of the mother and the development of the fetus, and the presence of the normal discomfort associated with pregnancy results in a high rate of abandonment of the treatment.

Ideally, a supplementation with a well accepted iron compound accompanied with educational information could improve the compliance of the supplementation resulting in a significant reduction in the prevalence of iron deficiency and iron deficiency anemia.

Brazil has endorsed the compromise to reduce by 30% the prevalence of iron deficiency during pregnancy before the year 2000 (6), and has made a great effort for the implementation of alternative, efficient measures that can be rapidly incorporated to the prenatal care programs, aiming at reaching the established goal of iron deficiency reduction in pregnancy.

Among the possible alternatives to control iron deficiency, iron bis-glycine chelate (Ferrochel) has been used and successfully evaluated in Brazil in iron fortified foods (13,14). As a supplement has been tested in other countries and has shown a great efficacy in reducing iron deficiency and iron deficiency anemia in very short-time treatments with significantly low doses (15).

Structurally, Ferrochel is a non-ionizable, non reducing compound of good stability that does not change the organoleptic characteristics of the foods in which it has been used as a fortificant. Formal testing using radiolabeled Ferrochel has shown the compound to have a high bioavailability, 4-7 times greater than that of ferrous sulfate, and that its absorption is regulated by the iron stores in the body (16).

The present study was designed to compare the efficacy of iron supplementation using ferrous sulfate or Ferrochel in the control of iron deficiency during pregnancy.

MATERIAL AND METHODS

The study was conducted in the community of Santo André in the State of Sao Paulo, Brazil. It was designed as a prospective longitudinal study in a cohort of 145 pregnant women that assisted to the prenatal control program in 6 of the 13 Basic Health Units that had the prenatal programs implemented.

The study was approved by the Ethics Committee of the Infant Assistance Foundation of Santo André (FAISA), that is the institution responsible for the public health services of the locality. The study was carried out in a random sample of pregnant women that volunteered to participate and that filled the following criteria: a). Less than 20 weeks of pregnancy as recorded in their clinical record, b). Low obstetric risk evaluated by absence of hypertension, diabetes and a number of set clinical criteria, and c). Non use of any iron supplement prior to the enrollment in the Pregnancy Attention Program (PAG). In 3 of the health posts, ferrous sulfate in a dose of 200 mg/day (40 mg iron), as recommended by the Ministry of Health of Brazil was given (7). In the other 3 health posts a supplement of 75 mg of Ferrochel/day (15 mg iron), was given considering that on the bases of bioavailability this lower dose was equivalent to the 40 mg of iron from ferrous sulfate. The final number of pregnant women per group of treatment is shown in Table 1.

TABLE 1
Composition of sample, time and source of supplement

Sample size	Supplement source	Elemental iron
74 pregnant women	Ferrous sulfate	40 mg/day
71 pregnant women	Ferrochel	15 mg/day

To prevent administrative factors, the supplements were guaranteed to all women starting from the 20th. week of pregnancy.

At the time of enrollment, each enrolled woman received a printed message on the importance of anemia and a form to register the daily intake of supplement, and in the case the supplement was not taken an explanation of the reason for non compliance. A copy of the supplement intake form was attached to the clinical record of each pregnant women, and was actualized after each visit.

At each visit, the attending physician reinforced the information to each women on the importance of the supplement for her health and that of the fetus. He/she personally supervised that the proper blood sample was taken for biochemical analysis when required.

Hematological measurements were carried out in three occasions: at the time of enrollment in the program (less than 20 weeks of pregnancy), between 20 and 29 weeks of pregnancy, and at 30 or more weeks of pregnancy. Blood was extracted from a cubital vein and dispensed into two tubes. One containing EDTA, was used for the photometric determination of hemoglobin by the cyanmethemoglobin procedure (17), and the other with no anticoagulant for the separation of serum for the determination of iron, total iron binding capacity, and ferritin by standard methods (18,19). From these data, transferrin saturation was calculated.

As suggested by WHO (20), the criteria used to establish the presence of anemia was a hemoglobin level lower than 11 g/dL. All pregnant women with ferritin levels below 12 µg/L were consider to be iron depleted (18), and all those with transferrin saturation levels below 16% were consider to be iron deficient (21).

Following the norm adopted by the Prenatal Attention Program, a supplement intake for least 13 weeks was considered satisfactory (7).

RESULTS AND DISCUSSION

About 15% of all pregnant women in the community of Santo André receive prenatal attention in the health centers. This means that about 1200 new pregnant women participate in the Prenatal Attention Program per year. Osis et al, commented that the majority of women participating of the public health centers in Brazil come from the population of lower familiar income and that this is the only service available to them (22), We confirmed that about 40% of the women studied referred an income of less than U.S. $ 100 per month. Sixty three percent of these women did not complete elementary school (8 years). Most of the sampled women that worked (20%) were employed in general services or did domestic chores. Over 20% of the sample studied was conformed by adolescent women (less than 20 years), and 42% were primiparas.

The mean number of prenatal visits to the clinics was 6 and about 30% did not attend the clinics with the minimum frequency considered adequate for the control of their pregnancy. This, of course, affected the total number of blood samples analyzed.

As stated before, good compliance in the supplement intake is affected negatively by a number of factors related to gastric effects, bad taste or administrative failure. The lack of supplement in the Basic Health Units, and the impossibility of the pregnant women to buy it locally are cited as the principal causes of non compliance in supplementation programs. Gillespie, et al, analyzing the supplementation programs in India, observed that over 80% of the treated women abandoned the program due to lack of supplement (23). Nuñez de Cassana (24) also describes similar reasons for non compliance.

To prevent this type of problem, in the present study the distributed supplements were always available and non compliance was then due to other factors. The adequacy of supplement intake was related to the type of supplement. Seventy three point two percent of the women treated with Ferrochel consumed the supplements for at least 13 weeks, while only 35.1% of those treated with ferrous sulfate reached the 13 week limit. This is shown in Table 2.

Table 3 presents the frequency of factors responsible for noncompliance as informed by the subjects.

TABLE 2
Adequacy of supplement intake as related to iron source

Type of Treatment	n	Adequacy of intake 13 weeks or more	Inadequate intake less than 13 weeks
Ferrous sulfate	74	26 (35.1%)	48 (64.9%)
Ferrochel	71	52 (73.2%)	19 (26.8%)

TABLE 3
Factors that affected compliance of the supplement as related to iron source

Factor	$FeSO_4$	FeAAC*
Nausea, womiting,diarrhea	5 (7.5%)	2 (2.9%)
Supplement's taste	20 (29.8%)	0 (0.0%)
Abandon of prenatal care	18 (26.9%)	14 (20.9%)
Abortion, change of address forgetfulness	5 (7.5%)	3 (4.5%)
Total	48 (71.6%)	19 (28.4%)

* FeAAC = Ferrochel

Faulty flavor was the principal factor of noncompliance in the group of women that consumed the ferrous sulfate supplement. In contrast in the Ferrochel treated group, none of the women reported faulty flavor. Twice as many women reported nausea, vomit or diarrhea as a cause of noncompliance when the supplement was ferrous sulfate than when it was Ferrochel.

One important factor to consider is that Ferrochel can be consumed with food without altering its bioavailability. This fact facilitates its use and may be a contributing factor for adequate intake of the supplement. Independent of the type of treatment, desertion of prenatal attention was the principal cause for noncompliance.

The principal cause of information loses was unexplained desertion from the prenatal program. A mean of 22% of the registered women stopped their periodic visits to the Program of Assistance to Pregnant women. Five point five percent reported change of address, fetal losses or plain forgetfulness for interrupting their assistance to the program.

Table 4 presents the mean values and standard deviations for hemoglobin and the iron deficiency indicators. From the second half of gestation, fetal and placental growth are responsible for the increased need of iron, and is at this stage that iron reserves may be depleted, and limitation in adequacy of diet intake become more apparent. Hemoglobin concentration is diminished up to the end of pregnancy. The table shows that hemoglobin response was similar in both treatments, but the response in terms of serum ferritin and transferrin saturation was much better in the groups that received Ferrochel treatment, in spite of the lower dose of iron from the chelate.

TABLE 4
Changes in concentration of hemoglobin and serum ferritin and on percent saturation of transferrin during pregnancy, as related to type of iron supplement

Gestational age	Hemoglobin, g/dL		Serum ferritin µg/L		Transferrin saturation %	
	$FeSO_4$	FeAAC*	$FeSO_4$	FeAAC*	$FeSO_4$	FeAAc*
<20 weeks						
mean ± s.d	12.3 ± 1.1	12.7 ± 1.0	38.0 ± 30.4	38.4 ± 35.1	29.2 ± 13.2	27.6 ± 13.0
(N)	(65)	(67)	(58)	(49)	(64)	(62)
20-29 weeks						
mean ± s.d	11.4 ± 0.7	11.9 ± 0.7	14.7 ± 10.5	24.8 ± 37.6	23.4 ± 13.7	27.9 ± 16.4
(N)	(40)	(33)	(33)	(24)	(37)	(29)
30 weeks or more						
mean ± s.d.	11.6 ± 1.3	11.9 ± 0.9	10.8 ± 8.1	14.3 ± 10.7	17.7 ± 11.1	22.8 ± 13.9
(N)	(30)	(25)	(20)	(20)	(28)	(28)

*FeAAC = Ferrochel. The sample size decreased as pregnancy progressed due to not attendance of some women for blood sampling and to losses of samples in the laboratories, as explained in the text.

The diagnosis of iron deficiency during pregnancy presents some difficulties due to the large intra-individual variation associated with the normal blood volume expansion during gestation. This may explain the large variability of the results obtained (25).

According to Milne, et al.(26), serum ferritin concentration is the most sensitive test for the identification of body reserves of iron. Furthermore, the decrease in ferritin confirms the etiology of the anemia.

Contrary to what has been described by Puolakka, et al. (27), a decrease in the levels of serum ferritin was observed which was more evident in the groups supplemented with ferrous sulfate. This drop in serum ferritin reflects an increase in blood volume and a rapid utilization of the body iron reserves which may become depleted during gestation, even in the absence of anemia.

Blood iron transport as measured by transferrin saturation also decreased being more marked in the ferrous sulfate supplemented group.

The importance of sample loss in spite of the ample information supplied to the women enrolled in the program has to be stressed. There was some resistance to blood drawing which became evident even in the first laboratory examination (< 20 weeks of pregnancy), this became more serious as gestation progressed. As can be appreciated in Table 3, only about one third of the enrolled women gave a blood sample at the third control (30 weeks of gestation or more).

All these arguments become more evident when one analyses only those women that in each group gave blood samples at the three different testing times. The sample was further reduced by sample losses in the laboratory. The results of this analysis are presented in Table 5.

This type of problem was also reported by Papagallo and Bull (28) who observed lowering compliance even when the only test they carried out was hemoglobin.

When one analyses only those women that have results for all the analysis from the basal sample to the last, Table 5, there is a clear difference in response to the treatments. At 30 or more weeks of pregnancy the better effectiveness of the smaller dose of Ferrochel is clear. None of the biochemical parameters measured was significantly reduced, while in the group using ferrous sulfate at higher dose this was not the case.Table 6 shows the distribution of the pregnant women sample as related to the presence of iron deficiency anemia or iron depletion according to the type of supplement ingested. Here again, the greater efficacy of the treatment with Ferrochel is evident, even when the dose was only about one third of the dose of ferrous sulfate.

Among women that did not consume adequately the supplement about 50% had anemia and practically all had iron depletion.

CONCLUSIONS

Desertion from the supplementation program is very common in the Brazilian public health services. In most cases medical consultation is related to pathological episodes and not by compliance with the established program to follow the normal development of pregnancy. This is specially true when blood collection data is analyzed since there is always a great resistance to blood sampling. This results in a significant reduction of the initial sample as was shown in Tables 3, 4 and 5.

The finding of low prevalence of iron deficiency in the first trimester of pregnancy is not frequent. Lack of compliance in attending the health services, in taking the assigned supplement, and in permitting blood sampling prevented the present study from reaching the starting goals. Nonetheless, the results obtained strongly point to a higher efficacy of the chelated iron (Ferrochel) for which acceptance was not a problem. We imaging that the greater compliance with the chelate may be due to the fact that the treatment can be taken with the meals causing less negative gastric effects.

TABLE 5
Changes in concentration of hemoglobin and serum ferritin and on percent saturation of transferrin during pregnancy, as related to type of iron supplement

Gestational age	Hemoglobin, g/dL		Serum ferritin µg/L		Transferrin saturation %	
	$FeSO_4$	FeAAC*	$FeSO_4$	FeAAC*	$FeSO_4$	FeAAc*
<20 weeks						
mean ± s.d	12.3 ± 1.09 ad	12.6 ± 1.00 b	41.7 ± 34.20 ce	43.2 ± 41.80	29.9 ± 12.0 f	27.6 ± 12.0
(N)	(23)	(14)	(21)	(7)	(22)	(13)
20-29 weeks						
mean ± s.d	11.4 ± 0.73 ad	11.9 ± 0.70 b	17.7 ± 10.50 c	16.5 ± 11.01	23.3 ± 13.0	27.3 ± 14.2
(N)	(40)	(14)	(22)	(14)	(22)	(14)
30 or more						
mean ± s.d.	11.6 ± 1.27	12.2 ± 1.02	10.7 ± 8.14 e	15.1 ± 10.10	17.7 ± 11.10f	22.0 ± 16.3
(N)	(23)	(14)	(17)	(11)	(21)	(13)

These data refers to all those pregnant women in the sample that completed the three blood samplings of the study. The differences in sample size are due to laboratory loses of sample.
The bars indicate which differences are statistically significant. For ferrous sulfate, Hb1 -Hb2 = 0.001; Hb1-Hb3 = 0.05. For Ferritin, For FeAAC, Hb1-Hb2 = 0.004. FeAAC = Ferrochel treated group.

TABLE 6
Presence of iron deficiency anemia or iron deficiency in pregnant women with 30 or more weeks of gestation, according to treatment and adequacy of supplement intake

Adequacy of intake	Treatment	Iron deficiency anemia	Iron depletion
Adequate	$FeSO_4$	2 (11.1%)	6 (54.5%)
	FeAAC*	0	4 (30.8%)
Inadequate	$FeSO_4$	6 (50%)	8 (88.9%)
	FeAAC*	3 (50%)	4 (100.0%)

* FeAAC = Ferrochel

ACKNOWLEDGMENTS

To the Ministry of Health of Brazil and to Albion Laboratories, Brazil, that provided the treatments with ferrous sulfate and Ferrochel, to Laboratorios Buenos Aires that prepared the supplements and to the Infancy Assistance Foundation of Santo André in whose centers the study was carried out.

REFERENCES

1. World Health Organization. The prevalence of anemia in women: a tabulation of available information. WHO. Geneva, 1992.
2. Klein L. Premature birth and maternal prenatal anemia. Am J Obstet Gynecol 1962; 83:588-90.
3. Klebanoff MA, Shiono PH, Selby JV, Trachtenberg AI, Graubard BI. Anemia and spontaneous preterm birth. Am J Obstet Gynecol 1991;164:59-63.
4. Scholl TO, Hediger ML, Fisher RL. Shearer JW. Anemia vs iron deficiency: increased risk of preterm delivery. A prospective study. Am J Clin Nutr 1992; 57:135-9.
5. Waller MF, Haynes EM. Effects of heat and exercise on sweat iron loss. Sci Sports Exerc 1996; 28:197-203.
6. Organización Panamericana de la Salud. Plan the acción para el control de la anemia por carencia de hierro en las Americas. OPS/OMS, Washington. D.C.,1996.
7. Secretaria de Estado da Saúde. Resolução SS131 de 16 de maio de 1990; establece diretrizes e estratégias para combater a anemia ferropriva. Diario Oficial do Estado de São Paulo 1990, 15 de maio; Secção 1, p 12.
8. Organización Mundial de la Salud. Lucha contra la anemia nutricional, específicamente contra la carencia de hierro. OMS, Informe Técnico 580. Ginebra, 1975.

9. Sood S, Ramachandran K, Marthur M, Gupta K, Ramalingaswamy V, Swarnabai C. et al. Word Health Organization sponsored collaborative studies on nutritional anaemia in India. Q J Med 1975; 44:241-58.
10. International Nutritional Anemia Consultative Group. Iron deficiency in women. Washington, DC: The Nutrition Foundation, 1981.
11. Charloenlarp P, Dhanamitta S, Kaewvichit R, Silprosert A, Suwanaradd C, Na-Nakorn S, et al. A WHO collaborative study on iron supplementation in Burna and Tailand. Am J Clin Nutr 1988; 47:280-97.
12. Schultink W, Van der Ree M, Matulessi P, Gross R. Low compliance with an iron supplementation program: a study among pregnant women in Jakarta, Indonesia. Am J Clin Nutr 1993; 57:135-9.
13. Fisberg M, Braga JAP, Klianca PE, Ferreira AMA, Berezowski M. Utilização do queijo petit suisse na prevenção da anemia carencial em pré-escolares. Clin Pediatr 1995; 6(19):27-31.
14. Torres MAA, Lobo NF, Sato K, Queiroz SS. Fortificação do leite fluido na prevenção e tratamento da anemia carencial ferropriva em crianças menores de 4 anos. Rev Saúde Públ 1996; 30:350-7.
15. Pineda O, Ashmead HD, Perez JM, Ponce-Lemus C. Effectiveness of iron amino acid chelate on the treatment of iron deficiency anemia in adolescents. J Appl Nutr 1994; 46:2-11.
16. Christensen JM. Effects of divalent amino acids on iron absorption. J Pharm Sci; 1984, 73(9): 1245-7.
17. Dacie JV & Lewis SM Practical hematology. Churchill Livingstone, 1984.
18. Fenton V, Cavill I, Fisher J. Iron stores in pregnancy. Brit J Haematol (1977); 37:145-9.
19. Behringwerke AG N Latex-ferritina. Edición Junio 1994.
20. Organización Mundial de la Salud. Anemias nutricionales. OMS.Ginebra. Informe Técnico 405, 1968.
21. International Nutrition Anemia Consultative Group. Measurements of iron status. Washington DC: The Nutrition Foundation, 1985.
22. Osis DMJ, Hardy E, Faunde A, Alves G. Fatores associados à assistência pré-natal entre mujeres de baixa renda no Estado de São Paulo, Brasil. Rev Saúde Públ 1993; 27(1): 49-53.
23. Gillespie S, Kevany J, Mason J. Controlling iron deficiency. Geneva: United Nations Administrative Committee on Coordinations. Subcommittee on Nutrition, 1991.
24. Nuñez de Cassana LM. Intervenção nutricional no controle da deficiência de ferro em gestantes da Rede Básica de Saúde [tesis]. São Paulo: Universidade de São Paulo - Faculdade de Saúde Pública, 1998.
25. Roodenburg AJC. Iron supplementation during pregnancy. Eur J Obstetr Reprod 1995; 61: 65-71.
26. Milne DB, Gallagher SK, Nielsen FH. Response of various indices of iron status to acute iron depletion produced in menstruating women by low iron status, intake, and phlebotomy. Clin Chem 1990; 36:487-91.
27. Puolakka J, Janne O, Pakarinen A, Jarvinen PA, Vihko R. Serum ferritin as a measurements of iron stores during and after normal pregnancy with and without iron supplements. Acta Obstet Gynecol Scand 1980; 95 (Suppl): 43- 51.
28. Pappagallo S and Bull DL. Operational problems of an iron supplementation programme for pregnant women. Bull World Health Organ 1996; 74:25-33.