The efficacy and tolerability of iron protein succinylate in the treatment of iron-deficiency anemia in pregnancy

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Summary

The aim of this study was to evaluate the efficacy and tolerability of iron protein succinylate in the treatment of iron-deficiency anemia in pregnancy. One hundred and thirty anemic pregnant women were studied. Inclusion criteria were iron-deficiency type of anemia, and hemoglobin levels below of 11.5, 10.9 and 10.3 g/dl for the three trimesters of pregnancy, respectively. Twenty-five women who presented pregnancy-related complications were excluded during treatment. The remaining 105 were treated with 1600-mg iron protein succinylate per os daily for a period of four months. A group of anemia-related clinical signs and symptoms, and hematological parameters were recorded at the beginning of treatment, as well as two and four months later. They included epidermis and mucosal paleness, skin and nail lesions, glossitis, heart pulse, sickness, anorexia, apathy, ataxia, polypnea, insomnia, nervousness, paresthesias and other neurological symptoms; the hematological parameters included Hgb, hct, RBCs, WBCs, MCV, MCH, MCHC, PLTs, serum Fe and ferritin. Possible side or adverse effects were considered during treatment. The majority of symptoms and signs of anemia were gradually improved. There was a statistically significant increase in the means of Hgb, hct, WBCs, MCV, MCH, PLTs and serum ferritin ($p < 0.05$). Anemia was effectively treated in 100/105 (95.2%) women, but not in five patients (4.8%) who displayed poor compliance to the therapeutic protocol. There were transient and mild side-effects in seven (6.6%) treated women, namely diarrhea, epigastralgia, vomiting, and nausea, which however, did not necessitate discontinuation of the therapeutic protocol. Iron protein succinylate is an effective and well tolerated treatment of iron-deficiency anemia in pregnancy.

Key words: Pregnancy; Iron deficiency anemia; Iron supplementation; Iron proteinsuccinylate.

Introduction

Anemia is one of the most common complications of pregnancy. The iron requirement of the developing fetus increases the demand for absorbed iron from 0.8 mg/day in early pregnancy to 7.5 mg/day in late pregnancy [1]. In addition, the insufficient food supply of iron in many countries as well as in some specific groups of pregnant women establishes iron-deficiency anemia as the most frequent type of anemia during pregnancy, accounting for more than 75% of the total cases [2]. Sideropenic as well as folate-deficiency megaloblastic anemia is more common in women who have an inadequate diet, and who are not receiving prenatal iron and folate supplements [3]. A World Health Organization committee recommended that hemoglobin (Hgb) values lower than 11 g/dl in the first and last trimester and 10.5 g/dl in the second trimester should be considered as the criterion of pregnancy-related anemia and diets must be supplemented with medicinal iron [4, 5]. The Center for Disease Control [6], the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists recommend the universal iron supplementation to meet the iron requirements of pregnancy [7].

Severe anemia in pregnancy may be associated with complications in both the mother and the fetus, such as increased susceptibility to infection, prematurity, low birth weight, and intrauterine growth retardation [8, 9]. Significant life threatening problems may arise with Hgb levels less than 6 g/dl [10, 11]. Thus, the diagnosis and sufficient treatment of anemia in pregnancy is important.

Although dietary recommendations may be helpful in preventing anemia during pregnancy, iron supplementation is necessary to cure iron-deficiency anemia. However, this treatment may aggravate the gastrointestinal disturbances of pregnancy, and a number of women demonstrate poor complicance [12]. Therefore, besides the efficacy, the tolerability of an iron compound medication is essential.

Iron protein succinylate (ITF 282, CAS 93615-44-2) is an iron succinyl casein complex, containing 5% iron in ferric form. This derivative, formed with iron bound to succinylated casein, precipitates in the stomach without releasing iron ions avoids gastric mucosa damage [13, 14]. Iron protein succinylate redissolves in the duodenum and makes iron available for absorption. These favorable observations have not been confirmed in the English literature in anemic pregnant women who need to be treated with iron supplementation. It may be important because gastrointestinal disturbances are common in pregnancy, and iron supplementation is given to the majority of pregnant women.

We examined the alterations occurring in anemia-related clinical and hematological parameters in pregnant women who were treated with iron protein succinylate. Both the efficacy of the therapeutic protocol and the tolerability of iron protein succinylate were evaluated.

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Materials and Methods

One hundred and thirty pregnant women with iron-deficiency anemia enrolled initially in the therapeutic protocol of iron protein succinylate supplementation. Twenty-five women dropped out during the therapeutic protocol because of the development of moderate or severe pregnancy-related complications. One hundred and five pregnant women with well-documented iron-deficiency anemia were ultimately enrolled in the study. In this final group anemia was diagnosed at the first, second and third trimester of pregnancy (43, 49 and 13 cases, respectively). The study was performed at the Department of Obstetrics and Gynecology, University Hospital of Heraklion, Crete, Greece from July 2001 until June 2003. The mean age of enrolled women was 25 years (SD = 5.86, range 16-40 years), the mean body weight was 69 kg (SD = 9.58, range 52-92 kg), and the mean body height was 164 cm (SD = 6.83, range 150-185 cm). The study was conducted with the approval of the Institutional Review Board, and informed consent was obtained from all treated women.

Inclusion criteria of enrollment in the study were the following: 1) well documented iron-deficiency type of anemia presenting during pregnancy; 2) absence of history of pre-existing anemia; 3) absence of any other chronic disorder with symptoms or signs that could interfere with the clinical course of anemia, or lead to misunderstanding of possible adverse side-effects of treatment. Particularly, women with gastrointestinal diseases, hemmorhagic diathesis, mechanical obstruction, acute or chronic diarrhea, and persistent vomiting were excluded. Cases with iron-deficiency anemia but with co-existence of features of hemolytic, aplastic or other types of anemia, as well as women who were receiving medication with an effect on hemopoiesis, were not included. Pregnant women with a "high-risk pregnancy" were excluded from the study. In addition, all the women that had initially enrolled but developed pregnancy-related complications such as hypertension, diabetes mellitus, moderate or severe hemorrhage, and infections were also excluded (25 individuals).

The characterization of anemia as iron-deficient was based on Hgb level, Hgb electrophoresis, mean corpuscular volume (MCV) and serum ferritin values. Hgb levels below 11.5, 10.9 and 10.3 g/dl were used as criteria for the diagnosis of anemia at the first, second and third trimester of pregnancy, respectively. Hgb value of 10.3 g/dl was also considered as the lower normal limit in puerperium. All women enrolled had MCV less than 82 fl, serum ferritin less than 12 μg/l and normal Hgb electrophoresis.

Iron protein succinylate was given orally before meals, in a dose of 800 mg twice a day (totally 1600 mg), for a total period of four months. In all treated women 5 mg of folic acid was also given daily to prevent both open neural tube defects and the megaloblastic anemia of pregnancy. Calcium supplements were also given in the standard recommendations. All women were informed about the symptoms and signs of anemia, as well as about the possible adverse or side-effects of iron supplementation.

In order to evaluate the severity of anemia and the efficacy of iron supplementation, the following clinical symptoms and signs were examined: epidermis and mucosal paleness, skin and nail lesons, glossitis, heart pulse, sickness, stomatitis, anorexia, apathy, ataxia, polypnea, insomnia, nervousness, paresthesias and other neurological manifestations. All these clinical manifestations were characterized by a grade "absent", "mild", "moderate" or "severe". The hematological parameters taken into consideration for assessing the treatment efficacy were: Hgb, hct, red blood cell (RBC) count, white blood cell (WBC) count, MCV, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT) count, serum iron and ferritin levels. Follow-up included a thorough clinical examination at the completion of two and four months of treatment, with simultaneous measurement of the hematological parameters. Systolic and diastolic blood pressure as well as heart rate of the pregnant women were also considered during treatment.

Statistical analysis

The package SPSS with 7.5 (for Windows) was used. The t-test for paired samples was used for statistical analysis of the alterations in hematological parameters during treatment. Statistical significance was set at $p < 0.05$. The non-parametric Wilcoxon matched-pairs and signed-ranks test were used for statistical analysis of the alterations in clinical manifestation of anemia during treatment.

Results

The response to treatment was estimated at the completion of the second and the fourth month of the therapeutic protocol. The treatment was effective in 100 out of 105 (95.2%) enrolled anemic pregnant women, as indicated by the correction of Hgb concentration to normal for pregnancy levels. In five women (4.8%) there was not successful treatment because of poor compliance to the iron supplementation. Fifteen women delivered during the therapeutic protocol, and therefore the last follow-up was carried out postpartum.

Table 1 shows the alterations in clinical symptoms and signs of anemia during the iron protein succinylate supplementation. Totally, there was progressive improvement in the manifestation of the anemia-related symptoms and signs. However, a statistically significant change ($p < 0.05$) was observed only in the epidermis and mucosal paleness, anorexia, apathy, and insomnia. The mean arterial blood pressure and mean heart rate value were not remarkably changed during treatment, and were retained constantly within normal clinical range.

Table 2 depicts the alterations occurring in the hematological parameters during treatment. It shows the mean ± SD, and the range of Hgb, hct, MCV, MCH, MCHR, RBCs, WBCs, PLTs, serum Fe and ferritin at the beginning of iron supplementation and at the completion of two and four months of treatment. Table 2 also shows the statistical significance of the differences between the means of examined parameters during treatment. At the completion of the therapeutic protocol there was a statistically significant increase ($p < 0.05$) in the means of Hgb, hct, MCV, MCH, WBCs, PLTs and serum ferritin, but not in RBCs and serum iron levels. There was a 0.54 g/dl increment in Hgb mean at the first two months of treatment, and 1.02 g/dl at the end of the protocol. At the completion of treatment 89 women (78 pregnant in the third trimester and 11 postpartum) had Hgb values greater than 10.3 g/dl, which is the lower normal Hgb value for the third trimester of pregnancy and puerperium (Figures 1a, b, c). The remaining 11 women (7 pregnant and 4 postpartum) displayed Hgb values between 9.25-

Table 1. — *Alterations observed in clinical symptoms and signs of anemia in pregnant women after two and four months of iron protein succinylate supplementation. P_1 P_2 P_3: the statistical significance of the alterations between: pretreatment and two months after treatment (P_1); two and four months after treatment (P_2); pretreatment and four months after treatment (P_3).*

	Pretreatment			P_1	After two months of treatment			P_2	After four months of treatment			P_3
	Absent	Mild	Moderate		Absent	Mild	Moderate		Absent	Mild	Moderate	
Epidermis paleness	42	50	8	.1683	46	52	2	.0021	63	37	0	.0002
Mucosal paleness	57	39	4	.0151	71	27	2	.1075	78	21	1	.0009
Sickness	80	17	3	.1578	85	15	0	.8313	84	16	0	.4405
Anorexia	42	55	3	.1440	53	46	1	.0020	73	27	0	.0001
Apathy	93	6	1	.1797	96	4	0	.0679	100	0	0	.0277
Ataxia	99	1	0	1.000	100	0	0	1.000	100	0	0	1.000
Tachypnea	95	4	1	.7353	95	5	0	.3613	97	3	0	.7353
Insomnia	46	51	3	.0362	59	40	1	.2950	66	34	0	.0070
Paresthesias	98	2	0	.4227	98	2	0	.1088	100	0	0	.5930
Nervousness	44	48	8	.2374	53	41	6	.5347	58	36	6	.1149

Table 2. — *Alterations in hematological parameters of pregnant women treated with iron protein succinylate: mean, standard deviation (SD), and range at the initiation of therapy (pretreatment), the 2nd, and the 4th month of treatment. P values show the statistical significance of differences between means: pretreatment and two months after treatment (P_1); two and four months after treatment (P_2); pretreatment and four months after treatment (P_3). ($p = 0.000$ is equal to $p < 0.001$).*

	Pretreatment			P_1	After two months of treatment			P_2	After four months of treatment			P_3
	Mean	SD	Range		Mean	SD	Range		Mean	SD	Range	
Hgb (g/dl)	10.71	0.53	9.8-11.8	.000	11.25	0.8	9.5-13.2	.000	11.73	0.96	9.4-14	.000
Hct (%)	33.1	1.63	29-36	.002	33.7	1.93	29-36	.000	34.60	1.87	28-37	.000
MCV (fl)	82.97	4.74	72-100	.977	83.02	5.79	65-100	.000	86	4.86	70-98	.000
MCH (pgr)	27.24	1.61	24-32	.365	27.51	2.62	20-35	.000	28.87	2.20	20-35	.000
MCHC (g/dl)	32.1	2.02	28-37	.016	31.10	3.61	19-37	.008	32.10	3.72	16-38	.850
RBCs ($x10^6/mm^3$)	4.75	0.53	3.8-5.9	.929	4.76	0.70	3.2-7.2	.143	4.89	0.62	2.7-6.2	.154
WBCs ($x10^6/mm^3$)	8.60	1.03	4.6-11	.000	9.60	1.51	7.0-15.2	.750	9.90	1.59	6-17.5	.000
PLTs ($x10^6/mm^3$)	2.39	0.75	1-4.2	.028	2.63	0.79	0.8-4.2	.144	2.75	0.67	1.1-5.2	.000
Fe (μg/dl)	78	47.9	17-280	.545	81.50	29.47	10-178	.390	79	24.44	10-175	.875
Ferritin (μg/lt)	36.50	23.66	10-102	.025	44.20	24.13	2-130	.005	53.80	29.21	10-139	.000

10.3 g/dl. Not one woman had a Hgb concentration lower than 9.6 g/dl at admission to the study. The lowest Hgb levels recorded during treatment were 9.38 g/dl and 9.25 g/dl at the second and third follow-up, respectively. We did not observe severe clinical manifestations of anemia and consequently, there was not requirement for any additional intervention (IV iron administration or blood transfusion). The mean of hct increased progressively from 33.1% to 33.7% (two months treatment) and finally to 34.6% (Table 2). Figure 2 (a, b, c) illustrates the distribution of MCV (mean ± SD) of the treated women at the beginning of protocol, two months later, and at the completion of the study. Figure 3 (a, b, c) similarly illustrates the distribution of serum ferritin concentration.

Seven pregnant women (6.6%) displayed adverse or side-effects that were attributed to iron supplementation. Specifically, three women had diarrhea that was intermittent and mild in two cases, and moderately but short in the last one. Two women complained of epigastralgia, and two others had episodes of nausea and vomiting. These complications occurred during the first two months of iron supplementation in five out of seven cases, and during the last two months of treatment in the remaining two cases. The necessity of treatment discontinuation did not arise in any treated woman, however in three of them a temporary decrease of iron dosage (at 800 mg daily) was recommended. No case of allergy to the iron protein succinylate was observed.

Discussion

The increased fetal and maternal demand for iron during pregnancy, inadequate dietary intake, occult hemorrhage, and diminished gastrointestinal absorption contribute to be the iron-deficiency anemia as the more common type of anemia in pregnancy [2]. Severe anemia during pregnancy is a well-known and considerable risk factor for both mother and fetus [15]. Fetal consequences are an increased risk of growth retardation, prematurity, intrauterine death, amnion rupture and infection. Maternal consequences of anemia are also well known and include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, tiredness, reduced peripartal blood reserves and finally increased risk for blood transfusion in the postpartum period [16]. Therefore iron supplementation is necessary when iron-deficiency anemia is diagnosed. However, not uncommonly, pregnant women show poor compliance in

Fig. 1.a

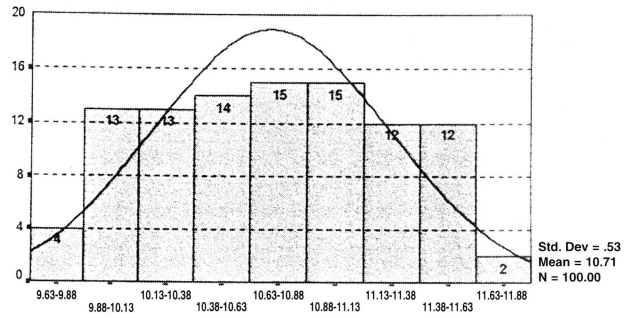


Fig. 1.b

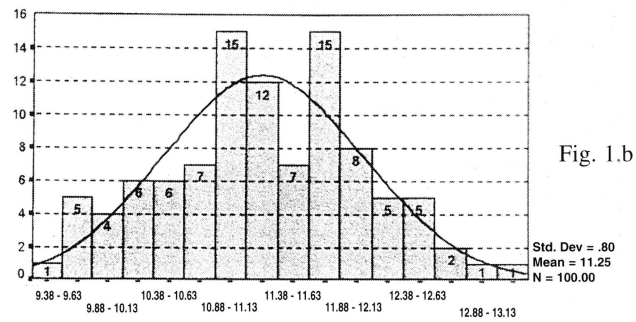


Fig. 1.c

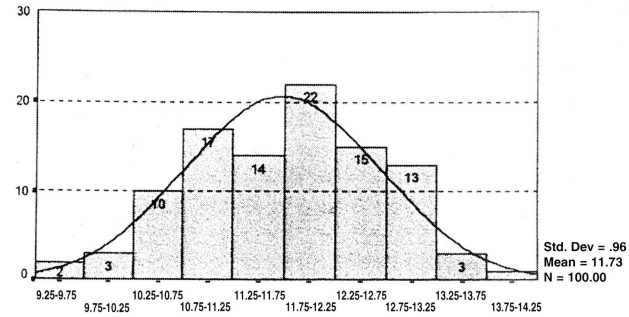
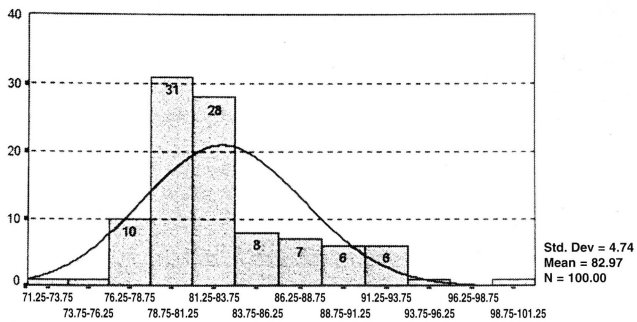


Figure 1a, b, c — The distribution, and the mean ± SD of Hgb concentration in treated women (a): before treatment; (b): after two months of treatment; (c): after four months of treatment.

Fig. 2.a



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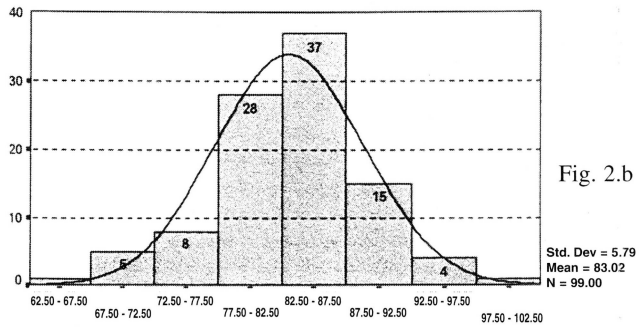


Fig. 2.c

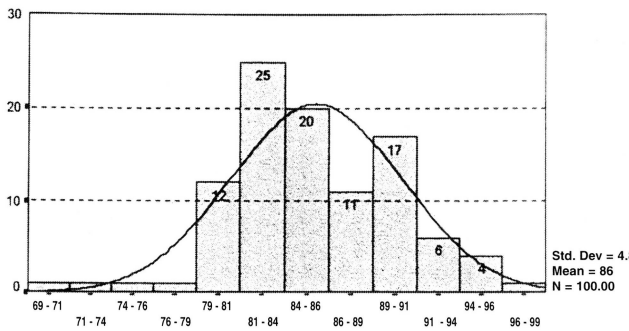
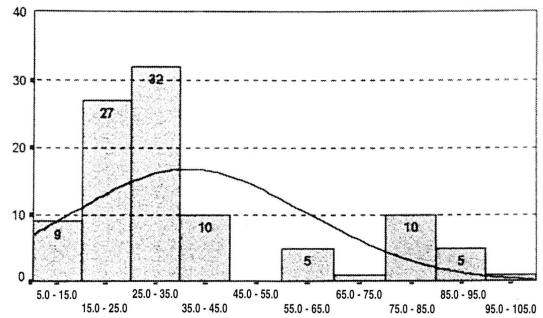


Figure 2a, b, c — The distribution, and the mean ± SD of MCV in treated women (a): before treatment; (b): after two months of treatment; (c): after four months of treatment.

treatment with iron medications [12]. This is due to a variety of reasons, such as the lack of health-care provider and patient perceptions that iron supplements improve maternal and infant outcomes, complicated dose schedules, and uncomfortable side-effects [17, 18]. Ingested iron may irritate the gastrointestinal tract, and abdominal cramps, diarrhea, constipation, and nausea are frequent patient complaints.

Iron protein succinylate is an iron compound without severe gastrointestinal side-effects. It keeps iron bound in the stomach and does not allow its release, avoiding the irritation of gastric mucous membrane. Iron is released in the intestine where it may have better absorption [19]. It is believed that iron protein succinylate demonstrates better tolerability compared with iron salts [20]. We examined the efficacy and tolerability of iron protein succinylate in pregnant women with iron-deficiency anemia, and this study is the first in the English literature.

The most precise method for measuring iron absorption and the activity of an iron medication might be the measurement of the total body radioactivity after a single dose of the iron labeled with the radioactive element. However, this kind of investigation is not practicable in pregnancy because of the contraindication of radioiso-



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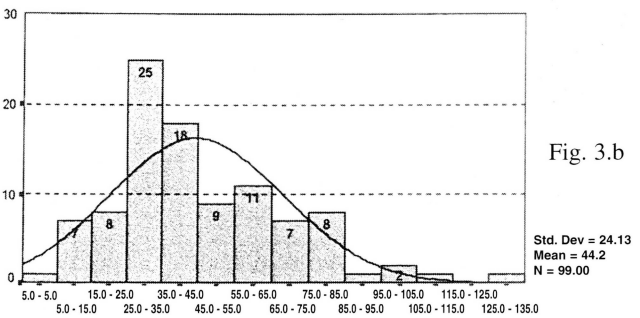
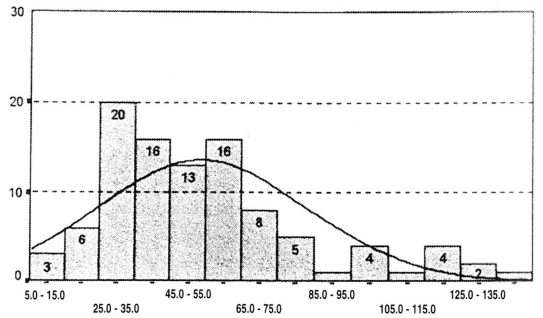


Fig. 3.b



g. 3.c

Figure 3a, b, c — The distribution, and the mean ± SD of serum ferritin concentration in treated women (a): before treatment; (b): after two months of treatment; (c): after four months of treatment.

topes. In this study the efficacy of iron protein succinylate was determined by the consecutive evaluation of the clinical manifestations of anemia, and by measurement of the alterations occurring in several hematological parameters. A thorough statistical analysis was used to examine the significance of these alterations.

All women included in this protocol showed a remarkable improvement in the clinical manifestations of anemia. However, it was statistically proven in only about half of the examined symptoms and signs; especially the clinical manifestations which were not closely related to anemia only displayed a positive trend of improvement and not a statistically significant change. It is probable that signs and symptoms, such as sickness, tachypnea and nervousness may not be related only to anemia. Different clinical conditions that complicate pregnancy may account for these manifestations, and an overlapping should always be taken into consideration. On the other hand, the most characteristic clinical features of anemia (epidermis, mucosal paleness) showed a significant and rapid improvement.

We consider that the most objective and reliable index of adequate anemia treatment is a statistically significant increase of Hgb levels, and secondarily an increase of hct, MCV, and serum ferritin levels. MCV displayed more satisfactory responsiveness to treatment compared to MCH and MCHC which may be explained by the definite "iron-deficient" type of anemia in the women treated in this study. Serum iron levels did not change significantly during treatment, probably because the iron supplement increased the production of RBC counts and satisfied fetal demands. Since the iron serum level changes after supplementation of different iron compound medications it is not a reliable measure for comparative studies. On the other hand, serum ferritin concentration is considered to be a more sensitive marker of responsiveness to treatment [21]. We observed a rapid increase of ferritin during our therapeutic protocol. Iron protein succinylate may cause a faster increase of Hgb, hct, MCV and ferritin levels than other iron medications [22]. The increased level of WBC counts observed in our study may not be related to the iron supplementation but simply to an expected pregnancy alteration. However, we are not able to adequately explain the relatively significant increase in PLT count, or to speculate about a possible association with the therapeutic protocol.

A few side-effects were observed in our patients, however, they were mild and temporary, and did not lead to poor compliance. Most side-effects were related to the gastrointestinal tract and were exactly those typically induced by iron treatment. However, what was remarkable was the absence of women complaining about constipation – possibly the most common side-effect of iron supplementation. All side-effects disappeared either spontaneously or after a transient dosage readjustment. The unsuccessful treatment of anemia in five patients was attributed to poor compliance, which however, was not correlated with any adverse effects of iron supplementation. Our results are in accordance with reports showing a better tolerability of iron protein succinylate in anemic patients [23, 24]. We confirm a sufficient tolerability in our anemic pregnant population.

Despite the remarkable and rapid clinical improvement that was observed during treatment, it should be emphasized that the majority of the enrolled women were not severely anemic, and they did not present severe clinical manifestations. In addition, these women were not in a high-risk pregnancy, and they did not develop severe

complications. Moreover, their daily dietary iron intake was estimated to be within a normal range for healthy adults, thus there were no aggravating factors of anemia. We believe that the therapeutic protocol used in this study should also be tested in pregnant women with more severe anemia and/or coexistence of other pregnancy-related complications, as well as in women with low-dietary iron intake.

As a conclusion, iron protein succinylate in a dosage of 1,600 mg daily per os is an effective and well-tolerated medication for the treatment of iron-deficiency type of anemia during pregnancy. Further studies are required to evaluate its efficacy and tolerability in more severe cases of anemia, as well as in high-risk pregnant women.

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