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Iron deficiency anemia in pregnancy: comparison of intermittent versus continuous ferrous sulfate scheme.

Anemia ferropénica en el embarazo: esquema de sulfato ferroso intermitente en comparación con el continuo

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Abstract

OBJECTIVE: The goal of the present study was to compare hemoglobin concentrations in pregnant women with iron deficiency anemia, who received 200 mg of ferrous sulfate in an intermittent treatment vs a continuous treatment. Additionally, we compared the frequency of side effects of the intermittent versus the continuous scheme.

MATERIALS AND METHODS: Randomized non-blinded clinical trial**.** The study was carried out at the Specialty Medical Unit, Obstetrics and Gynecology Hospital No. 4 *Luis Castelazo Ayala*, IMSS. The analyzed population was a group of patients between 18 and 35 years of age, with 30 weeks of pregnancy or more, from January to March 2023. The patients had a diagnosis of iron deficiency anemia (defined by a complete blood count under 11 g/dL, with hypochromia and microcytosis). The patients did not have a history of chronic degenerative disease. The statistical analysis was made with SPSS v21, a univariate analysis was made for the distribution and sample characteristics, followed by a bivariate analysis with the t of Student test, and a difference of means. A value of $p < 0.05$ was considered significant.

RESULTS: Thirty-two patients were studied: 16 following the continuous scheme and 16 the intermittent scheme. Both groups had an increase of 1 g/dL between the initial and final hemoglobin ($p < 0.01$), with a $p = 0.4$ for the difference of means. A significand decrease was observed in epigastric pain and nausea for the intermittent group .

CONCLUSIONS: The ferrous sulfate intermittent treatment increases hemoglobin concentrations just like the continuous scheme, but with fewer side effects.

KEYWORDS: Hemoglobin; Complete blood count; Iron deficiency anemia; Pregnant women; Ferrous sulfate; Intermittent scheme.

Resumen

OBJETIVO: Comparar las concentraciones de hemoglobina en embarazadas con anemia por deficiencia de hierro que recibieron un tratamiento intermitente en comparación con el continuo de 200 mg de sulfato ferroso por vía oral. Además, comparar la frecuencia de efectos secundarios del tratamiento intermitente con el continuo.

MATERIALES Y MÉTODOS: Ensayo clínico, aleatorizado, no cegado, efectuado en la Unidad Médica de Alta Especialidad Hospital de Ginecoobstetricia 4 Luis Castelazo Ayala, IMSS, en pacientes de 18 a 35 años atendidas entre los meses de enero a marzo del 2023 con 30 o más semanas de embarazo, diagnóstico de anemia ferropénica (definida operativamente solo con una biometría hemática inferior a 11 g/dL, con hipocromía y microcitosis), sin antecedentes de enfermedad crónico-degenerativa. El análisis estadístico se procesó en el programa SPSS v21, la distribución y características de la muestra con análisis univariado, seguido de un análisis bivariado con t de Student y diferencia de medias. Se consideró con significación estadística el valor de $p < 0.05$.

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RESULTADOS: Se estudiaron 32 pacientes: 16 con esquema continuo y 16 con el intermitente. Ambos grupos con incremento de 1 g/dL entre la hemoglobina inicial y final ($p < 0.01$), con una diferencia de medias entre el aumento de los grupos con $p = 0.4$. Con disminución significativa de la epigastralgia y la náusea.

CONCLUSIONES: El tratamiento intermitente con sulfato ferroso incrementa las concentraciones de hemoglobina igual que un esquema continuo, pero con menos efectos adversos.

PALABRAS CLAVE: Hemoglobina; biometría; anemia ferropénica; embarazadas; sulfato ferroso; régimen intermitente.

BACKGROUND

Pregnancy is one of the most intense metabolic states in a woman's life, given its high demand of energy and oxygen. This higher demand includes iron, especially in the last trimester, which is a period when this mineral's demand increases as much as six-fold in comparison to a non-pregnant woman's demand.[1,2,3]

Iron deficiency anemia implies a decrease of more than 10% of the total amount of erythrocytes, because of the drop of circulating hemoglobin and erythrocyte mass. During pregnancy, because of the physiological changes, the diagnosis is made when hemoglobin concentrations are below 11.0 g/dL.[4,5,6]

Anemia is classified according to severity, depending on hemoglobin grams:[7] mild, under the lower normal level down to 11 g/dL; moderate, values between 7 to < 9 g/dL; severe, < 7 g d/dL and under 6 g/dL as life-threatening.

The prevalence of iron deficiency anemia is higher in developing countries than in developed countries. The WHO calculates that in countries with medium to low income, 52% of pregnant women have anemia, while in countries with high income, the prevalence is of around 20%.[4] In Mexico, the prevalence of iron deficiency anemia in 2008, in non-pregnant women was of 15.6% and of 20.6% in pregnant women.[8] The causes of anemia during pregnancy are various, and in order of frequency they are: iron deficiency, blood loss, intestinal parasites, folic acid deficiency, bone marrow alterations, hormonal disorders, infections, or chronic diseases.[7,9] However, 98% of anemias in pregnancy, caused by insufficiencies, are due to iron deficiency.[2]

The diagnosis is clinical, and it is confirmed with a full blood count to determine the erythrocyte count (RBC), hemoglobin (Hb), hematocrit (HCT), RBC indices , reticulocyte, white blood cell, and platelet count. RBC indices determine the size or mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).[1,5,8] Iron deficiency anemia is detected in microcytic, hypochromic erythrocytes, normal or diminished reticulocytes (hyporegenerative), in serum iron, low transferrin saturation index[10], and low ferritin (< 30 ng/mL) which reflects body iron stores.[11]

The treatment includes changes in diet, and mineral and vitamin supplements, but it is indispensable to identify and address the root cause. Anemia improvement and the restitution of iron stores can be achieved with simple iron compounds: ferrous fumarate, sulfate, or gluconate,

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which provide around 200 mg/day of elemental iron.[12,13,14]

Currently, there are several schemes for oral or parenteral administration, with a tendency to modify classic schemes of daily administration to intermittent or weekly schemes, which can be ferrous sulfate, gluconate, or fumarate.[15-18] The treatment must always be personalized in order to find the best adherence. The amount of iron that a pregnant woman needs is 800 mg, of which 300 mg go directly to the fetus, and the remaining 500 mg are used for the additional synthesis of hemoglobin that covers the normal expansion of the mother's erythrocyte mass.[3-5,15]

The American College of Obstetricians and Gynecologists recommends the preventive administration of 30 mg of elemental iron (150 mg ferrous salts daily) beginning at the second trimester and continuing up to lactation. When the treatment is effective, the hemoglobin concentrations increase in the following three weeks of treatment, and the reticulocytes start to improve at 5 to 7 days, with a peak at 10 to 14 days.[3] The adverse effects of iron supplements are: nausea, constipation, epigastric pain, feces darkening, and diarrhea.[3,12,19]

The main goal for this study was to compare hemoglobin concentrations in pregnant women with anemia due to iron deficiency, these patients received intermittent treatment versus continuous treatment of 200 mg of daily oral ferrous sulfate. A secondary goal was to compare the frequency of side effects of the intermittent and the continuous treatments.

MATERIALS AND METHODS

Randomized, non-blinded clinical trial, carried out at the Specialty Medical Unit, Obstetrics and Gynecology Hospital No. 4 Luis Castelazo Ayala, IMSS. The subjects were pregnant women between 18 and 35 years, seen between January and March 2023, with 30 or more weeks of pregnancy. They had a diagnosis of iron deficiency anemia (with an operational definition of complete blood count [CBC] below 11 g/dL, with microcytosis and hypochromia), without a chronic degenerative disease. The exclusion criteria were patients with iron treatment, or with medication known to alter iron absorption, and the elimination criteria were patients who suspended the iron treatment and death.

A sample of consecutive pregnant patients with iron deficiency was made with the authorization of the hospital research and research ethics committees (CLIS1306).

The sample size was calculated with 16 cases per group, assuming a mean hemoglobin of 12 mg/dL ± 1 mg/dL, post-treatment with 200 mg of oral ferrous sulfate every 24 h, and a mean of 13 mg/dL ± 1 mg/dL, after treatment with 200 mg of oral ferrous sulfate every 48 h, with an alpha of 0.05, and 80% power.

Patient assignation to each group was made with the generation of randomized numbers on http://www.alazar.info/includes/show_data.php?operacion=nsr&cantidad=32&start=1&end=32.

After selecting the patients who met the inclusion criteria and signed the informed consent form, they were assigned to an oral treatment scheme: 200 mg of ferrous sulfate continuously (every 24 h) or intermittently (every 48 h). The treatment lasted 4 weeks and a CBC was made at the beginning for control, and another CBC was made after the treatment. The patients were interviewed to standardize their recording of date and time of intake, as well as to be informed of side effects.

All the patients received the indication of taking the medication with 100 mL of orange juice, in fasting, and preferably, at the same time each time.

After the data recollection, the statistical analysis was made with SPSS v21 software, the sample distribution and characteristics were analyzed with univariate analysis, followed by a bivariate analysis with the t of Student test, and mean difference. A p value of < 0.05 was considered statistically significant.

RESULTS

Two groups with 16 patients each were compared: one following a scheme of 200 mg of oral ferrous sulfate every 24 h, and the other with an equal dosage, but in an intermittent scheme, every 48 h. According to the Shapiro-Wilk test, the study population had a normal distribution in all the analyzed variables. The univariate analysis showed a mean age of 27 years, with a range of 18 to 35 years. The weeks of pregnancy distribution was between week 21.2 and 28.6, with a mean of 24. Previous pregnancies were between 1 and 5, with a mode of 2 pregnancies. The initial mean hemoglobin was 9.83 g/dL (± 1.07), and a value of 10.90 (± 1.13) g/dL after 4 weeks of treatment. **Table 1**

The comparison between the two groups, with the t of Student test showed no difference between the age of the two groups of mothers, the weeks of pregnancy, the number of previous pregnancies, nor the initial or post-treatment hemoglobin. The values of initial and post-treatment hemoglobin in the continuous group were 9.81 g/dL and 10.86 g /dL, respectively, while for the intermittent group the values were 9.85 g/dL and 10.93 g/dL. **Table 2**

Table 1. Basal characteristics of the population

Variable, n	32
Age, years, mean (SD)	27.06 (5.05)
Pregnancy weeks, mean (SD)	24.59 (4.60)
Pregnancies, mode (Range)	2 (1-5)
Initial hemoglobin, g/dL, mean (SD)	9.83 (1.07)
Final hemoglobin, g/dL, mean (SD)	10.90 (1.13)

SD: standard deviation.

The bivariate analysis showed a value of $p < 0.01$ through a difference of means between the initial and post-treatment hemoglobin of the continuous and intermittent groups, with an increase in the continuous group , and of 1.1 g/dL in the intermittent group (**Figure 1**). The comparison between the mean hemoglobin increase of the control and the intermittent groups had a $p = 0.4$.

The reported adverse effects for the patients with the continuous treatment were: epigastric pain in 11 of the 16 patients, nausea in 7 of 16, and constipation in 3 of 16 patients. In the patients of the intermittent group, they were in the same order, 3 of 16, 2 of 16, and 2 of 16 patients, with a significance of 0.004, 0.04, and 0.06, respectively. **Table 2**

DISCUSSION

The symptoms of anemia and pregnancy are often similar, so the suspicion and diagnosis of decrease of hemoglobin can be delayed, and thus increase perinatal fetal-maternal morbidity and mortality. As anemia and the progression changed, complications were also modified: death rate from 19.7 to 70 deaths per 10,000 births, or increase low weight at birth, premature birth, low fetal reserve, fetal distress, in the placenta there can be higher weight up to compensatory hyperplacentosis. [2,3,6]

Because pregnancy is a proanemic state, the treatment during this period has to be oriented to the correction of anemia, and the restoration of iron stores, which can be achieved with a daily average of 200 mg of elemental iron.[12,18] The best option is a low dosage of 40 to 80 mg of elemental iron once a day, or in alternating days. This can help to prevent ferritin values of ≤ 20 ng/dL, which indicate an inminent anemmic state. A higher dosage is not recommended because

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Table 2. Comparison between continuous and intermittent group

Variable, n	Continuous 16	Intermittent 16	p*
Age, years, mean (SD)	28.06 (5.07)	26.06 (4.90)	0.08
Gestational age, weeks, mean (SD)	25.06 (4.30)	24.10 (4.90)	0.06
Number of pregnancies, mode (range)	2 (1-4)	2 (1-5)	0.3
Initial Hb, g/dL, mean (SD)	9.81 (1.06)	10.86 (1.17)	0.4
Post-treatment Hb g/dL, mean (SD)	9.85 (1.11)	10.93 (1.13)	0.8
Epigastric pain, n	11/16	3/16	0.004
Nausea, n	7/16	2/16	0.04
Constipation, n SD: standard deviation.	3/16	2/16	0.6

* t of Student test.

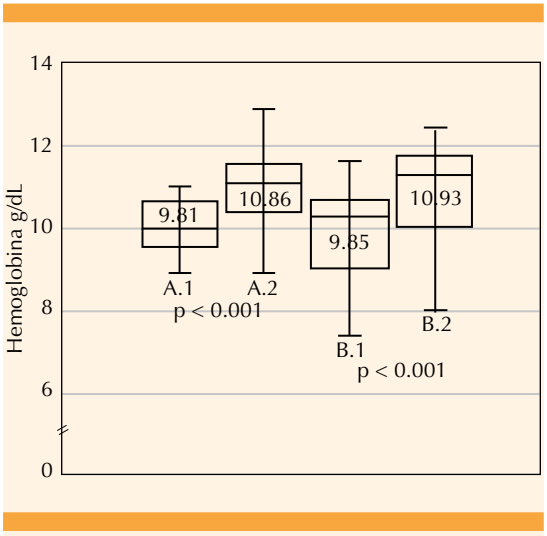


Figure 1. Comparison of means of pre- and post-treatment hemoglobin in the continuous and intermittent groups.
A: Continuous treatment: A.1 Pre-treatment hemoglobin, A.2 post-treatment hemoglobin. **B:** Intermittent treatment: B.1 Pre-treatment hemoglobin, B.2 post-treatment hemoglobin. The significance between the initial and final value of each group. The significance between the value of the group with continuous treatment and the continuous treatment had a p = 0.4.

it increases serum concentrations of hepcidin, which reduce iron absorption.[13,16,19]

Although the outcomes of oral intermittent and continuous schemes with 200 mg of ferrous sulfate are widely documented, the comparison between these treatments in a Mexican population allowed us to corroborate that the intermittent and continuous schemes are equally effective to increase hemoglobin in 1 g/dL per month of treatment (p = 0.4), with a difference in the proportion of adverse effects associated to the intake of oral iron, favoring the intermittent scheme, with similar reports in the literature.[13,16,20]

The comprehensive care of pregnant women is a global priority, but that doesn't mean that every place has access to the same diagnostic and therapeutic resources. The results reported here did not have the benefit of an iron kinetics study, which is ideal for the diagnosis of iron deficiency. We did have a CBC, which is a basic and accessible procedure worldwide, and its analysis allows the establishment of the diagnosis of iron deficiency anemia.[10]

It is clear that the different presentations and schemes of dosage of the supplements to treat anemia have a direct effect on the concentrations of hemoglobin, which administered in a timely manner, contribute to improve the

maternal-fetal perinatal effects, and optimize care costs. Besides knowing the supplement to be administered, and the equivalence and availability according to geographic region,[21,22,23] the ones with least side effects have to be identified, as it is the case of the intermittent scheme, which favors a better adherence to the treatment throughout the pregnancy.

CONCLUSIONS

The oral treatment with 200 mg of ferrous sulfate, in an intermittent scheme, shows no difference in hemoglobin increase with the continuous scheme, but it does show fewer side effects.

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