

Iron therapy in iron deficiency anemia in pregnancy: Intravenous route versus oral route

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OBJECTIVE: The aim of this study was to compare intravenous iron sucrose versus oral iron sulfate in anemia at 6 months of pregnancy.

STUDY DESIGN: A random, prospective, open study with individual benefit was performed involving 50 patients with hemoglobin levels between 8 and 10 g/dL and a ferritin value of <50 µg/L. In the intravenous group (IV group), the iron dose was calculated from the following formula: Weight before pregnancy (kg) × (120 g/L – Actual hemoglobin [g/L]) × 0.24 + 500 mg. The oral group (PO group) received 240 mg of iron sulfate per day for 4 weeks. Treatment efficacy was assessed by measurement of hemoglobin and reticulocytes on days 8, 15, 21, and 30 and at delivery and of ferritin on day 30 and at delivery. The baby's birth weight and iron stores were noted. Results were expressed as median ± interquartile range. Mann-Whitney and Wilcoxon tests were used for the analysis, with $P < .05$ considered significant.

RESULTS: An increase in hemoglobin was observed, rising from 9.6 ± 0.79 g/dL to 11.11 ± 1.3 g/dL on day 30 in the IV group and from 9.7 ± 0.5 g/dL to 11 ± 1.25 g/dL on day 30 in the PO group (not significant). On day 30 ($P < .0001$) and at delivery ($P = .01$) ferritin was higher in the IV group. A mean higher birth weight of 250 g was noted in the IV group (not significant).

CONCLUSION: Iron sucrose appears to be a treatment without serious side effects indicated in correction of pregnancy anemia or iron stores depletion. (Am J Obstet Gynecol 2002;186:518-22.)

Key words: Clinical study, pregnancy anemia, intravenous iron sucrose, oral iron sulfate, relative biologic and clinical effectiveness

Anemia is frequently observed during pregnancy. It occurs in 10% to 30% of pregnant women in mainland France and more frequently in the immigrant population.¹ Iron deficiency, which depends on the nutritional state of the patient,¹ is the principal cause.

Anemia exposes women to an increased risk of blood transfusion during the peripartum period² because the parturient can no longer cope with physiologic blood losses of delivery, let alone those associated with hemorrhagic delivery. The risk is equally increased by conditions that incur chronic bleeding during gestation, such as placenta previa.^{2,3}

Homologous blood transfusion may be difficult in pregnant patients who have highly unusual erythrocytic phenotypes and alloimmunization. These cases may benefit from scheduled autologous blood transfusion,^{4,6} but this cannot be correctly carried out if the patient's iron stores are limited and where the patient's iron requirement is increased by the fetoplacental unit.⁷

Systematic iron supplementation during pregnancy has been debated in France.⁸ However, treatment of iron deficiency anemia by administration of an iron supplement is codified. Long-term oral treatment can produce side effects, especially digestive ones, which can lead to noncompliance. Parenteral administration by intramuscular injection is a painful alternative with a variable degree of efficacy. Intravenous iron treatment with iron sucrose is available and is already in use in a number of European countries. Only one study has compared intravenous iron sucrose with oral iron treatment during pregnancy,⁹ with the former treatment producing better results.

The aim of this study was to compare the efficacy and tolerance of intravenous iron supplementation with iron sucrose (Venofer; Vifor International, Ltd, St Gallen) to those obtained by oral supplementation with iron sulphate Robapharm, Boulogne in iron deficiency anemia detected at 6 months of pregnancy, at the time of statutory red blood cell count.

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Table I. Anthropometric and biologic data for mothers and neonates in IV and PO groups

	<i>IV group (n = 24)</i>	<i>PO group (n = 23)</i>	<i>P value</i>
Mothers			
Age (y)	25 ± 4.5	25 ± 8	NS
Weight (kg)	55 ± 12	53 ± 18	NS
Parity (primiparous/multiparous)	10/14	10/13	NS
Gestational age on inclusion (wk)	25 ± 5	26 ± 3	NS
Hemoglobin level (g/dL)	9.6 ± 0.8	9.7 ± 0.5	NS
Mean corpuscular volume (fl)	86.2 ± 11.5	89.8 ± 11.7	NS
Reticulocyte count (10 ⁶ /mm ³)	0.095 ± 0.05	0.075 ± 0.03	NS
Ferritin level (µg/L)	6.5 ± 2.5	8.0 ± 4.0	NS
Transferrin level (g/L)	3.9 ± 1	4.1 ± 0.9	NS
Saturation coefficient (%)	9.0 ± 10	10.0 ± 8	NS
Erythrocytic folates (ng/mL)	450 ± 256	387 ± 395	NS
Neonates			
Gestational age (wk)	37 ± 2	37 ± 1	NS
Weight (g)	3595 ± 785	3220 ± 570	NS

No significant difference according to Mann-Whitney test. *NS*, Not significant.

Material and methods

This random, prospective, open study with individual benefit was supported by the Nancy Regional Maternity Hospital after acceptance by the hospital committee on clinical research. It was approved by the Advisory Committee for Protection of Persons in Biomedical Research at the Nancy Teaching Hospital. Patients' written consent was required. The study took place over a period of 15 months.

The study population consisted of 50 patients >18 years old with a hemoglobin level between 8 and 10 g/dL at 6 months of pregnancy. Other inclusion criteria were a mean corpuscular volume <100 fl and a ferritin level <50 µg/L, which corresponds to an iron store of <500 mg; the requirement of the third trimester of pregnancy is estimated at 600 mg.⁸ Patient exclusion criteria were anemia not linked to iron deficiency, asthma, cirrhosis, viral hepatitis, multiple pregnancy, risk of premature birth, suspected acute infection, parenteral iron treatment before inclusion, and intolerance to iron derivatives. Patients with transport difficulties, difficulties in comprehension of the guidelines of the study, who did not give their consent, and who had participated in a clinical trial during previous month were also excluded.

Patients were assigned to 2 groups of 25 by a randomization table. This group size was calculated from α risk of 5%, with a power of 95% on the basis of published data^{10,11} and according to the hypothesis that 20% of patients treated with oral iron would reach a hemoglobin level of 12 g/dL and that 20% of patients receiving intravenous iron would not reach 12 g/dL.

In the intravenous group (IV group), the total iron sucrose dose to be administered was calculated from the following formula: $\text{Weight} \times (\text{Target hemoglobin} - \text{Actual hemoglobin}) \times 0.24 + 500 \text{ mg}$, rounded up to the nearest multiple of 100 mg. The weight was the patient's weight

before pregnancy in kilograms; target hemoglobin in grams per liter was set at 120 g/L because of physiologic hemodilution during pregnancy; actual hemoglobin in grams per liter was the patient's hemoglobin level on inclusion; 0.24 was a correction factor that take into account the patient's blood volume, estimated at 7% of body weight and hemoglobin iron content; 500 mg is the quantity of stored iron in adults.¹²

This dose was given in 6 slow intravenous injections (on days 1, 4, 8, 12, 15, and 21). A maximum of 200 mg of iron (2 ampules) was administered over 5 minutes per ampule, using a small catheter, into a vein of sufficient caliber. For the first injection, 25 mg was injected very slowly and the patient was monitored during 15 minutes for signs of intolerance such as an anaphylactoid reaction or hypotension, phenomena previously observed with iron dextran administration. If the dose exceeded 200 mg per injection, iron was administered by slow infusion, with each 100 mg diluted in 100 mL of an isotonic sodium chloride solution, over a minimum period of 1.5 hours for 300 mg. Treatment was stopped either after administration of the calculated dose or once the hemoglobin level had reached 12 g/dL. Fifteen milligrams of folic acid (Speciafoldine, Theraplix, Paris) was systematically associated with the treatment to prevent an eventual folic acid deficiency and to eliminate the influence of such a deficiency on the results. Additional oral administration of iron was excluded during the 4 weeks of study.

The group receiving oral treatment (PO group) received three 80-mg iron sulfate tablets (Tardyferon) (ie, a total of 240 mg of elemental iron per day for 4 weeks). This treatment was also supplemented with 15 mg of folic acid per day. Patients were required to carefully note treatment compliance on a calendar provided for that purpose.

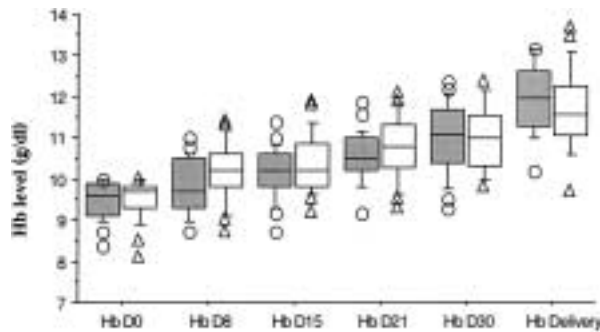


Fig 1. Change in hemoglobin (Hb) level, intravenous group (open circles and gray boxes) versus oral group (open triangles and white boxes). Mann-Whitney test. Data points, median, error bars, interquartile range.

After 4 weeks, in the 2 groups the duration and dose of continuing oral treatment was decided by the personal physician or midwife.

The 2 groups were monitored both clinically and biologically. On each visit, adverse reactions linked with or likely to be linked with the treatment were identified. This ensured that all incidents were noted, such as arterial hypotension during injections, tachycardia, hyperthermia, arthralgia, abdominal pain, a sensation of chest tightness, headache, vertigo, digestive problems, skin eruption, allergic reactions, and a strange taste during injection. After delivery, data were also noted: date of delivery (weeks of gestation) and baby's birth weight. Postpartum events particularly signs of anemia and blood transfusions were also recorded.

Biologic monitoring was carried out at various times. On inclusion (day 0), in addition to data required at the start of the study, the following measurements were recorded: mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, transferrin level, transferrin saturation coefficient, and erythrocytic folates. On days 8, 15, 21, and 30 the red blood cell count and reticulocyte count were recorded. On day 30, at the end of study, the ferritin level, transferrin level, and transferrin saturation coefficient were also recorded. On arrival at the delivery room, a maternal blood sample was taken for a red blood cell count and ferritin level. At birth, the baby's iron status was evaluated by measure of the ferritin level and a full blood cell count on blood taken from the umbilical vein.

Statistics software used was Statview (Abacus Concepts, Inc, Berkeley, Calif). Results were expressed as median \pm interquartile range. Because the spread of results was not normally distributed, nonparametric tests were used in the statistical analysis of data, the Mann-Whitney test for comparisons of nonpaired series, and the Wilcoxon test for comparisons of paired series. Variations of $P < .05$ were considered to be statistically significant.

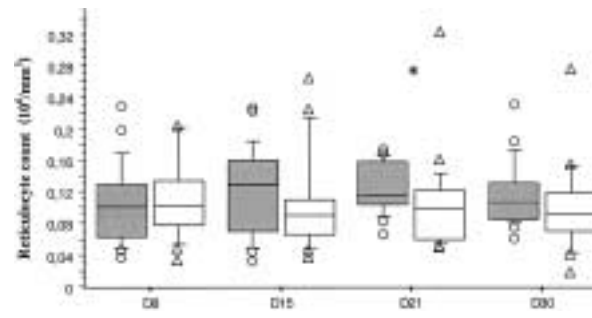


Fig 2. Change in reticulocyte level, intravenous group (open circles and gray boxes) versus oral group (open triangles and white boxes). Mann-Whitney test; asterisk, $P = .027$. Data points, median, error bars, interquartile range.

Results

The study involved only 47 patients because 3 were excluded during the study. One of these patients, with an initial diagnosis of iron deficiency anemia (ferritin 38 $\mu\text{g/L}$), was in the intravenous group, but because of ineffectiveness of the treatment on days 8 and 15, despite a sharp increase in ferritin levels, this diagnosis was revised. A hemolytic anemia was suspected and a hematologic advice was solicited. Iron sucrose administration was stopped to prevent accumulation. Two exclusions in the per os group were due to, in one case, a premature delivery 48 hours after inclusion and, in the other case, an absence of biologic monitoring between inclusion and delivery. Two of 47 patients included gave birth in another hospital, which explains the absence of their data concerning delivery and the neonate; in these cases, intermediate data were used.

On inclusion, the 2 groups were comparable in terms of both anthropometric and biologic data (Table I); there were no differences in either the median erythrocytic folate value or in the number of depleted patients. One patient in the PO group received a transfusion of 4 units of packed red blood cells immediately after delivery because of postpartum hemorrhage from placenta accreta. In contrast, one patient in the IV group was not given a blood transfusion after postpartum hemorrhage from uterine atonia, despite having a hemoglobin level of 6.3 g/dL, because the patient had a cardiovascular stability and a sufficient iron store, with a ferritin level of 393 $\mu\text{g/L}$ at delivery, to cope with such anemia.

A clear increase in hemoglobin was observed in the 2 groups, rising from 9.6 ± 0.79 g/dL to 11.11 ± 1.3 g/dL on day 30 in the IV group and from 9.7 ± 0.5 g/dL to 11 ± 1.25 g/dL on day 30 in the PO group (not significant [NS]). The 2 groups showed no differences in hemoglobin level at any time (Fig 1). Three patients reached the hemoglobin target in the IV group and 4 in the PO group on day 30. Mean corpuscular volume, mean corpuscular

hemoglobin, and mean corpuscular hemoglobin concentration increased in both groups (NS). Reticulocyte counts also increased (Fig 2), but the difference was not statistically significant until day 21, in favor of the IV group ($P = .027$).

On day 30, there was a highly significant difference in ferritin levels between the 2 groups with iron reserves restored only in the IV group ($P < .0001$). This difference, although less significant ($P = .01$), was observed up until delivery (Fig 3). A fall in transferrin level was noted in both groups on day 30 (NS), with a simultaneous increase in the transferrin saturation coefficient (NS).

In the IV group the only adverse reaction reported by the patients was the appearance of a not-unpleasant taste during injection. No patients reported pain on intravenous injection. In the PO group only one patient interrupted treatment because of diarrhea. Unfortunately, this was the only patient who required a transfusion. In the other patients, compliance controlled by investigators was excellent.

There were no weight differences between babies of the two groups at birth (Table I), although there was a mean difference of 250 g in favor of babies in the IV group. It should be noted that one macrosomic baby in the PO group was excluded from the statistical analysis (birth weight 5150 g). Neonates' biologic data were comparable in the two groups, with a hemoglobin level of 15.15 ± 2.10 g/dL in the IV group and 15.3 ± 2.17 g/dL in the PO group and a ferritin level of 132 ± 104 μ g/L and 134 ± 107 μ g/L, respectively.

Comment

Iron deficiency anemia during pregnancy is common and deserves special attention because of its potential consequences. Moreover, some pathologic situations increase the risk of hemorrhage and require a rapid restoration of iron reserves. In our study, contrary to results reported by Al-Momen et al⁹ under the same circumstances, iron sucrose does not seem to be more effective than orally administered iron in elevating hemoglobin levels during pregnancy. However, only iron sucrose appears to restore iron reserves in case of severe deficiency with a statistical difference at any time of the treatment period and even at the delivery several weeks after the end of intravenous treatment.

However, these two studies did not use the same method. First, regarding the total dose of iron sucrose, patients in the Saudi study received larger doses than our patients did, for several reasons. The weight at inclusion and not the one before the pregnancy was used in calculating the doses. Target hemoglobin set by Al-Momen et al was 13 g/dL and the factor they used in the calculation was 0.3, whereas we used 0.24, in accord with published data.¹² Finally, calculation of the dose required to restore iron reserves used weights of Saudi women, whereas we

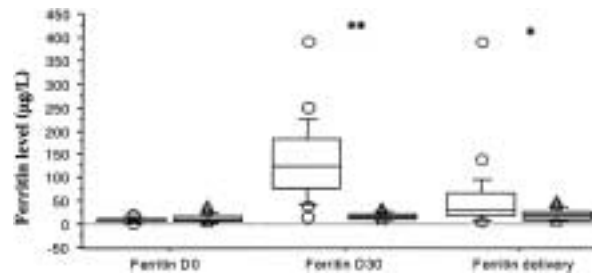


Fig 3. Change in ferritin level, intravenous group (open circles and white boxes) versus oral group (open triangles and gray boxes). Asterisk, $P < .01$, Mann-Whitney test; two asterisks, $P < .0001$. Data points, median, error bars, interquartile range.

used a constant defined for adults.¹² These differences reveal the importance of the weight factor in the results. Indeed, in our study only those patients whose weight before pregnancy exceeded ideal weight (calculated by Lorentz's formula) by $\geq 10\%$ reached target hemoglobin levels. In contrast, on day 30 the mean hemoglobin level in patients whose weight was ideal or lower by $\geq 10\%$ than the ideal weight were below target and proportional to their weight. Applying the same reasoning to the PO group receiving a constant dose shows that anemia was less well corrected in overweight patients and, inversely, better corrected in underweight patients.

A number of other differences between our study and the one carried out by Al-Momen et al should be noted. These include term on inclusion, parity, whether pregnancy was single or multiple, duration of pregnancy after inclusion, the rate of increase in hemoglobin, and compliance with oral treatment. These are all aspects that are likely to have an influence on results and that were not discussed in the Saudi study.

In our study, compliance with oral treatment was surprisingly good and contrasts with findings described in other studies. Gastrointestinal troubles, with a frequency up to 30% as described by Al-Momen et al⁹ have been reported in patient groups treated with oral iron. Patient information at inclusion regarding the importance of the iron treatment certainly accounts for the good compliance and results of the supplements in the PO group and the low incidence of digestive side effects. In practice, physicians are often faced with poor compliance, justified by digestive side effects that can lead to worsening anemia. In these cases the parenteral forms of administration are indicated, as well as those in which the oral treatment is ineffective.¹³ The same applies to patients with inflammatory bowel diseases, many of whom are iron deficient and show digestive intolerance to ferrous salts.¹⁴

Other situations where iron sucrose is indicated are those in which the iron stores may be depleted, such as in patients undergoing programmed autologous blood

transfusion⁷ or those with placenta previa,¹⁵ although the latter is debatable.¹⁶

Also, in this study the total iron sucrose dose was administered over 21 days, which is a relatively long period of time. This period can be shortened without surpassing the maximum intake of 600 mg per week recommended by the French Drug Agency.

This paves the way for other potential indications, such as anemia discovered late in the pregnancy or in patients who have low iron reserves and present a risk of hemorrhage during peripartum, such as in multiple pregnancy or overdistention of the uterus, in hope of avoiding a transfusion. This possibility should be explored. Finally, a difference in weight was observed between the two groups of neonates, with a higher birth weight (a mean difference of 250 g) in the iron sucrose group. Although the difference of 250 g is not statistically significant, it is clinically interesting because in a number of studies iron deficiency has been associated with low birth weight,¹⁷⁻¹⁹ in part linked to premature birth, which was excluded from our study. Furthermore, in our study only two neonates had a birth weight of <3000 g in the iron sucrose group compared with four in the oral treatment group, including one neonate who had a very low birth weight of only 1250 g. There is no other obvious explanation for this phenomenon because in our study there were no differences between the two groups in terms of duration of pregnancy, smoking habits, diabetes mellitus, or hypertension. However, the numerous factors involved in fetal growth renders interpretation of this result difficult. For this difference to be statistically significant, 90 patients are needed in each group, with a power of 90%, with babies weighing <2500 g being excluded. The number of patients in our study was therefore insufficient to be statistically significant.

Intravenous iron sucrose tolerance seems to be excellent in our study without adverse effect, in accordance with the literature.²⁰

Overall, iron sucrose appears to be a treatment of choice with no serious side effects indicated in the rapid correction of anemia in pregnancy or restoring maternal iron stores, especially because the total dose can be administered over a shorter period than that adopted in our study. If used in time, this treatment will certainly help reduce the risk of homologous blood transfusions during the peripartum period. The dose to be administered should take into account the ideal weight, the quantity required to restore iron reserves as evaluated by the ferritin level, and probably also the needs of the fetus. The effect of this treatment on size and weight of the developing baby should be investigated in further studies.

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