Intravenous Versus Oral Iron for Treatment of Anemia in Pregnancy

A Randomized Trial

Ragip A. Al, MD, Eylem Unlubilgin, MD, Omer Kandemir, MD, Serdar Yalvac, MD, Leyla Cakir, MD, and Ali Haberal, MD

OBJECTIVE: The aim of this study was to compare the efficacy of intravenous iron to oral iron in the treatment of anemia in pregnancy.

METHODS: In this randomized open-label study, 90 women with hemoglobin levels between 8 and 10.5 g/dL and ferritin values less than 13 μg/L received either oral iron polymaltose complex (300 mg elemental iron per day) or intravenous iron sucrose. The iron sucrose dose was calculated from the following formula: weight before pregnancy (kg) × (110 g/L – actual hemoglobin [g/L]) × 0.24 + 500 mg. Treatment efficacy was assessed by measuring hemoglobin and ferritin on the 14th and 28th days and at delivery, and the hemoglobin on the first postpartum day. Adverse drug reactions, fetal weight, hospitalization time, and blood transfusions were also recorded.

RESULTS: Hemoglobin values varied significantly with time between groups (interaction effect, $P < .001$). The change in hemoglobin from baseline was significantly higher in the intravenous group than the oral group at each measurement; the changes with respect to subsequent hemoglobin were significantly higher on the 14th ($P = .004$) and 28th ($P = .031$) days. Ferritin values were higher in patients receiving intravenous iron throughout pregnancy. No serious adverse drug reactions were observed. Fetal weight and hospitalization time were similar in the 2 groups. Blood transfusion was required for only one patient in the oral group.

CONCLUSION: Intravenous iron treated iron-deficiency anemia of pregnancy and restored iron stores faster and more effectively than oral iron, with no serious adverse reactions.
(Obstet Gynecol 2005;106:1335–40)

LEVEL OF EVIDENCE: I

From Division of Maternal-Fetal Medicine, Ankara Etlik Maternity and Women's Health Teaching Hospital, The Ministry of Health of Turkey, Ankara.

Corresponding author: R. Atakan Al, Cigdem Mah. 357. Sok, Segmen sitesi a Blok No 7/25, 06530 Karakusunlar, Ankara-Turkey; e-mail: atakanal@superonline.com.

ISSN: 0029-7844/05

High proportions of women in industrialized and developing countries develop anemia during pregnancy. Worldwide, iron deficiency is the most common cause of anemia in pregnancy. The first choice in the treatment of iron deficiency anemia for almost all patients is oral iron replacement because of its effectiveness, safety, and lower cost. Intravenous iron therapy is reserved for a small number of patients in whom oral treatment fails or for whom iron loss exceeds intake that can be met by oral therapy. Severe systemic adverse effects associated with iron dextran and iron gluconate limited the use of intravenous iron. Both iron dextran and iron gluconate cause unpredictable anaphylactic reactions and require a test dose before the first administration for treatment. However, iron sucrose is reported to be safe and effective for the management of anemia, and it can be administered without a test dose[1–3]

Anemia leads to an increased risk of blood transfusion during the peripartum period. Iron therapy before delivery may reduce the transfusion rate for the iron-deficient women.[4] However, there may not be enough time for the treatment of anemia until term. Iron dextran does not induce an erythropoietic response more rapidly than oral iron replacement while use of iron requires several weeks after administration of iron dextran. Thus, the rise in hemoglobin concentration is only slightly faster than that after oral iron treatment. In recent years, few studies compared intravenous iron sucrose treatment with oral iron treatment during pregnancy.[5,6] However, some controversies exist between these studies.

The purpose of the study was to compare the efficacy of intravenous iron sucrose (Venofer; Vifor AG, St. Gallen, Switzerland) with that of oral iron polymaltose complex (Ferrum Hausman Fort; Vifor AG) in iron deficiency anemia of pregnancy during third trimester.

MATERIALS AND METHODS

The study was an open-label, randomized controlled clinical trial carried out at Ankara Etlik Maternity and Women's Health Teaching Hospital in Ankara, Turkey. Approval was obtained from the institutional review board. Patients were recruited from the antenatal clinic of the hospital. Eligible participants were pregnant women, between the 26th and 34th weeks of gestation, with established iron deficiency anemia who had hemoglobin levels between 8 and 10.5 g/dL and ferritin levels less than 13 μg/ L. Women were excluded when serum folate and vitamin B12 levels were found to be less than 4 pg/mL and 100 pg/mL, respectively. Anemia from causes other than iron deficiency, multiple pregnancy, previous blood transfusion, history of hematological disease, risk of preterm labor, intolerance to iron derivatives, recent administration of iron for the treatment of iron deficiency anemia, or current usage of iron supplement were the reasons for other exclusions.

All eligible women who applied to the antenatal clinic of the hospital during the study period were invited to participate in the study; those who gave informed consent were consecutively enrolled. All were randomly assigned to either intravenous or oral iron treatment. Group allocation was predetermined by one of the authors who was not involved with patient care. Opaque envelopes were consecutively numbered by means of a computer-generated randomization table. As each patient gave consent for the study, the next envelope was opened to assign the patient to either of the 2 groups.

In the group of patients to whom iron was administered intravenously, the dose for total iron sucrose was calculated from the following formula: weight $\times$ (target hemoglobin – actual hemoglobin) $\times$ 0.24 + 500 mg, rounded up to the nearest multiple of 100 mg.[6] In the formula, weight represented the patient's weight before pregnancy in kilograms; target hemoglobin in grams per liter was set at 110 g/L. In each infusion, the maximum total dose administered was 200 mg elemental iron in 100 mL 0.9% NaCl, infused in 20–30 minutes. No test dose was given. Total dose was administered over 5 days and maximum daily dose administered was 400 mg elemental iron. Most of the patients received iron sucrose at the rate of 200 mg every other day. Treatment was completed after administration of the calculated dose. Additional oral iron was not administered during the study.

In the group of patients to whom iron was administered orally, three 100-mg iron tablets per day were given (ie, a total of 300 mg of elemental iron per day) throughout their pregnancy. Patients were instructed to take the tablets on an empty stomach, 2 hours before or after their meals. Both groups were supplemented by 0.5-mg folic acid treatment per day. Additional multivitamin or vitamin C preparations were not given during study.

Iron-sucrose infusions were administered in the perinatology unit at an outpatient setting, and all patients were observed for 1 hour after the infusions. All adverse events after each infusion of elemental iron were identified by physical examination and direct inquiry of each patient, using standard forms encoded for adverse events. Blood pressure was measured before, during, and after each infusion, and hypotension was recorded as an adverse event if it was clinically significant.

The primary outcome measure was hemoglobin concentration on day 28 and at birth. Secondary outcome measures included ferritin levels, the recorded adverse effects, and fetal birth weight. At the beginning of the study, all patients were seen every 2 weeks for laboratory tests and then followed up routinely in the antenatal clinic until delivery. During each visit, all adverse events related or possibly related to the drugs were recorded after physical examinations and direct inquiries of the patients. Adherence to oral treatment was assessed by the number of returned tablets. After delivery, pregnancy outcomes were obtained from each woman's medical records. These included type of birth, gestational age at birth, transfusion history, fetal birth weight, and hospitalization time.

Laboratory evaluation was performed at the time of inclusion in the study, on the 14th and 28th days, at birth, and on the first postpartum day. Initial evaluation included complete blood count, serum iron binding capacity, serum ferritin, folate, vitamin B12, peripheral smear, and stool hemoccult. On the 14th and 28th days and at birth, complete blood count and ferritin levels were determined. After delivery a complete blood count was obtained.

All laboratory tests were performed immediately after sampling. Complete blood counts were measured by AutoAnalyzer (Technicon H.3; Bayer AG, Leverkusen, Germany); serum iron-binding capacity and serum ferritin were measured by chromogen assay (AU640e Chemistry Immuno Analyzer; Olympus Medical Systems, Tokyo, Japan); and vitamin B12, folate, and ferritin levels were determined by immunochemiluminescence (ACS:180 SE Automated Chemiluminescence System for vitamin B12 and folate, Bayer Immuno 1 Immunoassay Analyzer for ferritin, Bayer AG).

A sample-size analysis was performed before

initiation of the study. We estimated standard deviation of hemoglobin values to be approximately 1.5 g/dL. Based on a 2-tailed α of .05, it was determined that 37 patients per group were required to detect a 1 mg/dL hemoglobin difference in the primary outcome variable with a power of 80%. On the assumption of an overall rate of loss to follow-up of 10–20%, 45 subjects per group were required.

The analysis was based on the intention-to-treat principle. Statistical software used for analysis was SPSS (SPSS 10.0 Incorporated, Chicago, IL). The Kolmogorov-Smirnov test was used to check the normality of distribution. Hemoglobin measurements were analyzed by repeated-measures analysis of variance (ANOVA) with Huynh and Feldt correction. Ferritin measurements across time within each group were analyzed by Friedman 2-way variance analysis, and paired comparison was performed by Friedman post hoc test.[7] Other statistical analyses were performed with χ^2 test, Student *t* test, and Mann–Whitney test, as appropriate. All significance tests were 2-tailed, with an α level of 0.05.

RESULTS

One hundred six eligible women were invited to participate in the trial between May 2004 and July 2004. Sixteen (15.1%) women declined to participate; 90 (84.9%) women were randomly assigned to receive either oral iron (n = 45) or intravenous iron (n = 45). No participants were lost to follow-up, and there were no dropouts. Blood samples and pregnancy data were available for all of the patients.

The back-count of tablets collected from women in the oral iron group showed that 40 (88.9%) women took more than 90% of their supplement daily. Only 5 patients (11.1%) took less than 50% of the tablets. All patients administered intravenous iron received the calculated total iron dose. The median dose administered was 600 mg (500–900 mg) of elemental intravenous iron.

Initial demographic and clinical characteristics were generally similar in the 2 groups (Table 1). A total of 20 patients (22.2%) (11 [24.4%] in intravenous versus 9 [20%] in orally administered groups; P = .612) had been given iron supplementation during early pregnancy. As described below, this potential confounder was further analyzed by excluding patients in whom iron supplement was previously given. None of the patients had been taking iron preparations within the previous 4 weeks at the time they were recruited. On follow-up, 2 patients developed hypertensive disorder of pregnancy in the intravenous group. One of them was admitted at the 40th week of gestation with severe preeclampsia. The other patient developed mild gestational hypertension at the 41st week. Both patients delivered vaginally without complications. In the oral group, 2 patients developed gestational diabetes. They required insulin treatment and delivered without complications. The patients who developed hypertension and gestational diabetes were not excluded from analysis.

The average hemoglobin values (± standard error of the mean) are shown in Figure 1. Hemoglobin values were different for patients in oral and intravenously administered groups (P = .001). When analyzed across time, the hemoglobin values were found to vary significantly within individual treatment groups (P < .001). A significant time × group interaction (P = .009) indicated that the serial hemoglobin values varied between groups. Patients with intravenously administered iron were significantly more

Table 1. Maternal and Infant Characteristics*

	Oral Iron	Intravenous Iron	*P*
Age (y)	26.5 ± 5.6	24.9 ± 5	.173
Weight (kg)	58.2 ± 10	56.0 ± 8.3	.270
Primiparous	19 (42.2)	28 (62.2)	.06
Gestational age on inclusion (wk)	28.9 ± 2.9	29.7 ± 2.9	.191
Gestational age at birth (wk)	39.1 ± 1.2	39.2 ± 1.5	.659
Hemoglobin (g/dL)	9.8 ± 0.6	9.9 ± 0.5	.387
Mean corpuscular volume (fL)	85.2 ± 8	86.9 ± 6.5	.278
Ferritin (μg/L)	5 ± 2.2	4.1 ± 2.5	.095
Serum iron (μg/dL)	45 (16–188)	43 (21–142)	.707
Serum iron binding capacity (μg/dL)	442.9 ± 81.4	450.9 ± 73	.622
Folate (ng/mL)	11.3 ± 3.2	9.9 ± 2.7	.027
Vitamin B12 (pg/mL)	197.5 ± 51.3	184.4 ± 35.5	.162
Cesarean	12 (26.7)	9 (20)	.455
Neonatal weight (g)	3,439 ± 451	3,498 ± 452	.538
Previous iron supplementation	9 (20)	11 (24.4)	.612

* Values are given as mean ± standard deviation, n (%), or median (min-max) where appropriate.

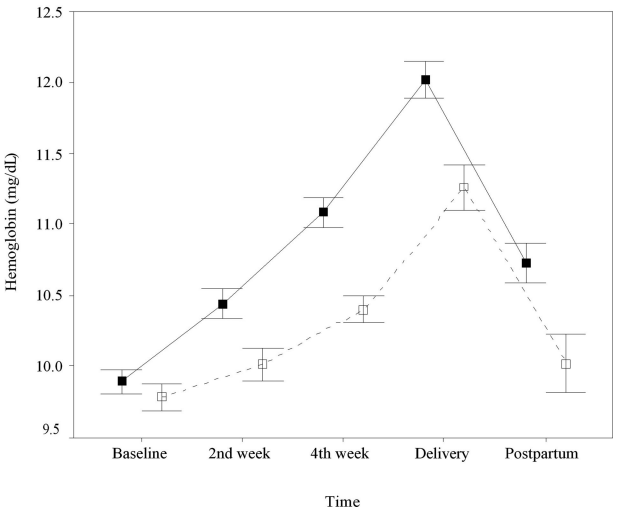

Fig. 1. Mean hemoglobin levels during study period (*straight line and black boxes*: intravenous iron; *dotted line and white boxes*: oral iron. Error bars represent standard errors).
Al. Intravenous Iron Treatment in Pregnancy. Obstet Gynecol 2005.

likely to have higher hemoglobin from baseline than those patients with orally administered iron at every point of measurement (Table 2). When mean hemoglobin of each week was compared to the mean of subsequent levels, the increase in hemoglobin was significantly higher in the intravenous iron group than that of the oral iron group at the second and fourth weeks (Table 3). The differences between the 2 drugs were due to a rapid hemoglobin increase after the drug was administered intravenously in the first month. Nine patients (20%) reached the hemoglobin target of 11g/dL in the oral iron group and 28 (62.2%) in the intravenous iron group at 4 weeks ($P < .001$). At birth, 28 patients (62.2%) reached the hemoglobin target of 11g/dL in the oral iron group and 43 (95.6%) in the intravenous iron group ($P < .001$).

Ferritin values were found to be changed significantly across time within both the oral ($P < .05$) and intravenous groups ($P < .05$). In the oral group, serum

Table 2. Hemoglobin Differences According to Baseline Hemoglobin

	Hb Differences		
	Intravenous Iron	Oral Iron	*P*
$Hb_{2nd\ week}–Hb_{baseline}$	0.6	0.2	.004
$Hb_{4th\ week}–Hb_{baseline}$	1.2	0.6	.000
$Hb_{delivery}–Hb_{baseline}$	2.1	1.5	.001
$Hb_{postpartum}–Hb_{baseline}$	0.8	0.2	.010

Hb, hemoglobin.

Table 3. Hemoglobin Differences According to Subsequent Measurement

	Hb Differences		
	Intravenous Iron	Oral Iron	*P*
$Hb_{2nd\ week}–Hb_{baseline}$	0.6	0.2	.004
$Hb_{4th\ week}–Hb_{2nd\ week}$	0.6	0.4	.031
$Hb_{delivery}–Hb_{4th\ week}$	0.9	0.9	.664
$Hb_{postpartum}–Hb_{delivery}$	1.3	1.2	.8

Hb, hemoglobin.

ferritin gradually increased throughout treatment (Fig. 2), and only the change in ferritin value between the second and fourth weeks was not significant in pairwise comparisons ($P > .05$). In the intravenous group, the change in ferritin value was significant between all ferritin measurements in pairwise comparisons ($P < .05$ for all comparisons). Serum ferritin decreased throughout treatment after the second week (Fig. 2). The serum ferritin value was higher in the intravenous iron group than in the oral iron group at each point of measurement (Fig. 2). It was 11 ± 11 μg/L compared with 28 ± 26 μg/L ($P < .001$) at the fourth week and 18.1 ± 11 μg/L compared with 23.7 ± 13.8 μg/L ($P = .04$) at birth in the oral and intravenous iron groups, respectively.

As stated above, 22.2% of the subjects received iron supplements in early pregnancy (Table 1). To eliminate a possible confounding effect of prior iron supplementation, we reanalyzed the repeated-measures by ANOVA,

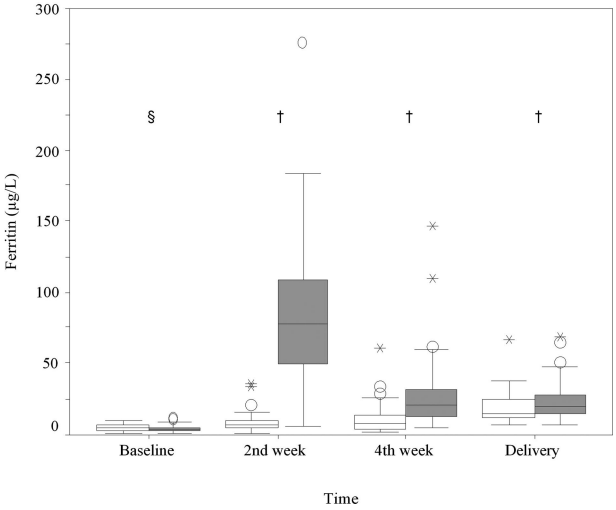

Fig. 2. Median ferritin levels during the study period (*gray boxes*: intravenous iron; *white boxes*: oral iron; data points, median, error bars, interquartile range, extremes (*), outliers (o); † $P < .001$, Mann–Whitney test; § $P = .095$, Student *t* test).
Al. Intravenous Iron Treatment in Pregnancy. Obstet Gynecol 2005.

excluding patients who were administered iron supplements previously. The time × group interaction remained statistically significant ($P < .001$), confirming the fact that the serial hemoglobin values vary between groups (oral compared with intravenous administered iron). When the change in hemoglobin was compared between groups, it was again higher from baseline in the intravenous iron group at each point. The difference in change of hemoglobin between groups remained statistically significant at the first month with respect to subsequent levels (data not shown). We also reanalyzed ferritin values by excluding the patients who were administered pretreatment iron supplements. Using the Friedman 2-way variance analysis, the change in ferritin across time remained significant in both oral ($P < .05$) and intravenous groups ($P < .05$), and the pattern of change was the same as the pairwise comparisons given above. Serum ferritin levels remained higher in the intravenous iron group than in the oral iron group at each measurement point (data not shown).

There was no significant difference between the mean birth weights of the infants in the 2 groups (Table 1). The median hospitalization time was the same in the 2 groups (2 [range 1–11] days in oral group versus 2 [range 1–6] days in intravenous group; $P = .9$). One woman who was given oral iron developed a vaginal hematoma after birth, and hemoglobin value dropped to 6.2 g/L from 10.4 g/dL. She received 2 units of packed red blood cells after delivery. No woman in the iron sucrose group received blood transfusion.

A total of 152 injections of 289 doses of iron sucrose were administered. There were no serious adverse drug reactions recorded, no episodes of anaphylaxis, no hypotensive attack, no patient withdrawals, and no drug discontinuation caused by drug-related adverse events. Adverse events possibly related to iron sucrose administration included a metallic taste (11 events), hot flush (12 events), arthralgia (1 event), dizziness (8 events), nausea (5 events), and vomiting (1 event).

During antenatal visits, 14 patients (31.1%) in the oral group experienced gastrointestinal symptoms. Thirteen patients (28.9%) complained of upper gastrointestinal symptoms (including epigastric discomfort, nausea, and vomiting), and 4 patients (8.9%) suffered from diarrhea that was managed with symptomatic treatment. No patient discontinued the drug because of gastrointestinal symptoms. In the intravenous group, 6 patients complained of upper gastrointestinal symptoms (13.3%) and one of arthralgia (2.2%). Incidence of gastrointestinal symptoms was significantly higher in patients given oral iron ($P = .04$).

DISCUSSION

This study confirmed that parenterally administered iron-sucrose elevates hemoglobin and restores iron stores better than oral iron polymaltose complex during the treatment of mild iron deficiency anemia of pregnancy. The mean hemoglobin and ferritin levels throughout the treatment were significantly higher in the intravenously administered iron group than in the orally administered iron group. The rise in the hemoglobin concentration was significantly faster than that observed with orally administered iron, and a significantly higher number of patients achieved the targeted hemoglobin at the fourth week and at delivery.

It is generally accepted that intravenous iron therapy induces a similar or slightly more rapid erythropoietic response than oral iron replacement.[8] This statement has been justified extensively by the results obtained with iron dextran treatments but may not be generalized for iron sucrose treatments. The rate of iron delivery to the marrow is a major factor in the regulation of marrow proliferation.[9] Iron dextran and iron sucrose have different pharmacokinetic properties. Iron sucrose complex has an intermediate stability and strength. It is quickly cleared from serum with a terminal half-life of approximately 5–6 hours compared with iron dextran, which has a serum half-life of 3–4 days. It is more rapidly available for erythropoiesis.[10–13] Intravenous iron sucrose produces a more rapid increase in hemoglobin concentration than oral iron and intramuscular iron dextran.[14] In the current study, maternal iron stores were restored more rapidly with intravenously administered iron than orally administered iron as reported in earlier studies.[5,6]

Iron sucrose was approved in the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis receiving supplemental erythropoietin therapy. Two studies compared iron sucrose with orally administered iron in the treatment of iron deficiency anemia in pregnancy.[5,6] al-Momen et al[5] reported findings similar to those in our study. They compared 52 women treated with intravenous iron sucrose with 59 women treated with 300 mg of oral iron sulfate and found that intravenous treatment resulted in higher hemoglobin levels in shorter periods compared with the oral treatment group. In their study, however, 30% of the patients had poor compliance with oral treatment, and the authors administered larger doses of iron sucrose than we did in the present study.

Bayoumeu et al,[6] however, reported comparable success with both oral and intravenous iron treatments

in elevating hemoglobin. In their study, 24 women given intravenous iron sucrose were compared with 23 women given 240 mg oral ferrous sulfate. Patient compliance in the oral iron group was reported as excellent. In general, we used a method similar to that used by Bayoumeu et al. However, there are differences between our study and the one carried out by Bayoumeu et al that might explain the different results. First, they administered the total iron sucrose dose over 21 days, which was relatively longer than our study. Second, the sample size of the study was smaller than that of our study. The success of oral iron treatment depends on various factors. Especially, the patient's dietary habits influence the success of treatment because the nature of the meal affects absorption. Absorption also decreases when iron is taken after or during meal. It is difficult to control these confounding factors even when good adherence to treatment is achieved. These confounding factors may be represented variously in small samples.

Iron sucrose was well tolerated with no serious adverse effects. It has a lower incidence of adverse allergic reactions, and death from anaphylactic events has not been reported yet.[3] Gastrointestinal adverse effects were more frequent in the oral group, as expected. Because daily folic acid supplements were given to all of the patients, possibly about 18% of the symptoms might be attributable to oral iron. However, most of the symptoms were mild, and no patient discontinued the medication.

The review by Williams and Wheby[15] notes that several studies considered anemia to be a risk factor for low birth weight. Fetal birth weight was not different between groups in the current study. The only blood transfusion was required in the oral treatment group. However, the study was not designed to address these clinical outcomes. The sample size is not sufficient to compare transfusion rates and fetal birth weights between the groups.

Pregnancy puts the women at risk of major peripartum blood loss, and women who have severe anemia constitute a high risk group for blood transfusions. There is no clear evidence from randomized trials to show whether clinical outcomes may be modified by using available treatments in women with iron deficiency anemia during pregnancy.[16] The choice of treatment of iron deficiency anemia is oral iron replacement because it is the safest and least expensive. However, it seems that intravenous iron sucrose is a safe and effective alternative to oral iron in treatment of iron deficiency anemia of pregnancy. It restores blood stores more rapidly, and a prompt increase in hemoglobin may be achieved. It may reduce the blood transfusion rates in pregnant women who have severe anemia near term. Major disadvantages of intravenous treatments are cost, need for hospitalization or an outpatient setting, and the invasive nature of the procedure. However, it may be considered an alternative to oral iron in the treatment of pregnant women with severe iron deficiency anemia during the third trimester.

REFERENCES

1. Van Wyck DB, Cavallo G, Spinowitz BS, Adhikarla R, Gagnon S, Charytan C, et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. Am J Kidney Dis 2000;36:88–97.
2. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol 2004;76:74–8.
3. Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. Am J Kidney Dis 1999;33:464–70.
4. Dickason LA, Dinsmoor MJ. Red blood cell transfusion and cesarean section. Am J Obstet Gynecol 1992;167:327–30.
5. al-Momen AK, al-Meshari A, al-Nuaim L, Saddique A, Abotalib Z, Khashogji T, et al. Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy. Eur J Obstet Gynecol Reprod Biol 1996;69:121–4.
6. Bayoumeu F, Subiran-Buisset C, Baka NE, Legagneur H, Monnier-Barbarino P, Laxenaire MC. Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route. Am J Obstet Gynecol 2002;186:518–22.
7. Siegel S, Castellan NJ. The case of k related samples. In: Nonparametric statistics for the behavioral sciences. New York (NY): McGraw-Hill, 1988:168-189.
8. Schrier S. Treatment of anemia due to iron deficiency. In: Rose B, editor. UpToDate. Wellesley (MA): UpToDate, 2004.
9. Hillman RS, Henderson PA. Control of marrow production by the level of iron supply. J Clin Invest 1969;48:454–60.
10. Danielson BG, Salmonson T, Derendorf H, Geisser P. Pharmacokinetics of iron(III)-hydroxide sucrose complex after a single intravenous dose in healthy volunteers. Arzneimittelforschung 1996;46:615–21.
11. Beshara S, Lundqvist H, Sundin J, Lubberink M, Tolmachev V, Valind S, et al. Pharmacokinetics and red cell utilization of iron(III) hydroxide-sucrose complex in anaemic patients: a study using positron emission tomography. Br J Haematol 1999;104:296–302.
12. Yee J, Besarab A. Iron sucrose: the oldest iron therapy becomes new. Am J Kidney Dis 2002;40:1111–21.
13. Charytan C, Levin N, Al-Saloum M, Hafeez T, Gagnon S, Van Wyck DB. Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. Am J Kidney Dis 2001;37:300–7.
14. Pritchard JA. Hemoglobin regeneration in severe iron-deficiency anemia: response to orally and parenterally administered iron preparations. JAMA 1966;195:717–20.
15. Williams MD, Wheby MS. Anemia in pregnancy. Med Clin North Am 1992;76:631–47.
16. Cuervo LG, Mahomed K. Treatments for iron deficiency anaemia in pregnancy (Cochrane Review). In: The Cochrane Library, Issue 2 2001. Oxford: Update Software.