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# Selective Use of Recombinant Human Erythropoietin in Pregnant Patients with Severe Anemia or Nonresponsive to Iron Sucrose Alone

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## Key Words

Anemia · Pregnancy · Iron deficiency · Iron sucrose · Recombinant erythropoietin

## Abstract

**Objective:** To evaluate the effectiveness of a stepwise use of recombinant human erythropoietin (rhEPO) in pregnant patients with severe anemia or nonresponsive to intravenously administered iron only. **Methods:** All subjects had iron deficiency anemia, i.e., a hemoglobin (Hb) level <10.0 g/dl and ferritin  $\leq 15 \mu\text{g/l}$ . Patients with an Hb level  $\geq 9.0$  g/dl and <10.0 g/dl received 200 mg iron sucrose intravenously twice weekly. If response to therapy was poor, patients additionally received 10,000 U rhEPO twice weekly. Patients with an Hb level <9.0 g/dl primarily received iron sucrose and rhEPO likewise. **Results:** Of the 84 patients, 59 had a baseline Hb level between 9.0 and 9.9 g/dl, of whom 32 responded poorly, thus receiving additional rhEPO. Twenty-five patients had a baseline Hb level <9.0 g/dl. The overall Hb level after therapy was 11.0 g/dl ( $\pm 0.5$ , range 10.0–12.6 g/dl). Mean duration of therapy was 3.5 weeks (7 infusions). **Conclusion:** This study shows an effective treatment regimen for patients with various degrees of anemia in pregnancy. Iron sucrose is a safe and effective treatment option. In cases of severe iron deficiency anemia or poor response to parenteral iron ther-

apy additional administration of rhEPO might be considered. However, the mechanism for not responding to intravenous iron therapy despite iron deficiency anemia still remains unclear to a large extent.

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## Introduction

Iron deficiency is the most common nutrient deficiency in the world and the most common cause of anemia in pregnancy. According to the WHO's World Health Report 2002, as many as 4–5 billion people, or 66–80% of the world's population, may be iron deficient, while 2 billion – over 30% of the world's population – are anemic, mainly due to iron deficiency [1].

The prevalence of gestational iron deficiency is 10–15% in industrial countries such as Switzerland, Germany, and the USA, rising to 50–75% in developing countries. But due to increasing migration the problem of iron deficiency anemia is to be rising in industrial countries.

The daily iron requirement in pregnancy is 4–5 mg, a figure which cannot be met even by increased intestinal absorption from an optimal diet. In other words, iron balance is inevitably negative in every pregnancy, shown by the continuous decline in serum ferritin levels to term [2].

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This can result in iron store depletion, which has a qualitative and quantitative impact on maternal erythropoiesis with the possible appearance of anemia. Gestational anemia carries several risks for the mother and the fetus. Depending on its severity, the risk of preterm delivery and low birth weight is elevated [3]. In the mother, in both pregnancy and the puerperium, when the problem is magnified by puerperal blood loss, iron deficiency anemia impairs performance and induces tiredness, headaches and dizziness. The WHO has estimated that anemia contributes to 20% of all maternal deaths [1].

Rapid and effective correction of anemia is thus a core target in obstetric management. As the efficacy of orally administered high-dose iron is limited by side effects and noncompliance, and blood transfusions are relegated to use as a final resort due to the risk of viral contamination and other potential complications [4], modern alternative strategies call for parenteral administration of well-tolerated iron preparations (e.g. iron sucrose).

Iron sucrose alone or in combination with recombinant human erythropoietin (rhEPO) has been successfully used in the treatment of anemia in pregnancy [5–8] as well as in the puerperium [9, 10].

We were able to demonstrate successful treatment of iron deficiency anemia in pregnancy with a combination of rhEPO and iron sucrose [5], but we are also aware of the mainly economic limitations of such a costly treatment regimen. Therefore, we set up a study protocol to discriminate between patients who might be in need of a combined therapy compared to treatment with iron sucrose alone. If anemia was more severe [hemoglobin (Hb) <9.0 g/dl], we decided to treat these patients with the most efficient combination of iron sucrose and rhEPO from the beginning of therapy. With this approach our aim was to set up a stepwise therapy scheme for an effective and rapid treatment of iron deficiency requiring intravenous administration of iron (sucrose). Hb was chosen as primary target as it is the most relevant for clinicians' daily routine.

## Materials and Methods

The hospital's institutional review board approved the study protocol. Patients gave informed consent before inclusion. Treatment was not started before 16 weeks of gestation and was continued for 4 weeks (i.e., 8 infusions or a maximum iron dose of 1,600 mg, according to calculated maximum iron deficit) or until the target Hb level of 11.0 g/dl was reached. Target Hb was chosen according to the CDC cutoff for anemia in the 3rd trimester [11].

### Inclusion Criteria

Subjects had iron deficiency anemia, i.e., an Hb level <10.0 g/dl and a ferritin level  $\leq 15 \mu\text{g/l}$ . All patients had received oral iron supplements (80 mg iron sulfate daily) on a routine basis since the beginning of the second trimester, but developed anemia. Minimum duration of oral iron supplementation was 4 weeks, before intravenous therapy was commenced.

### Exclusion Criteria

Women with anemia from causes other than iron deficiency (e.g. infection, chronic bleeding or renal failure) or previous blood transfusions, with a history of hematologic disease (e.g. thalassemia or sickle cell disease) or a history of iron or rhEPO intolerance were all excluded.

### Study Groups

All patients were recruited on a consecutive and prospective basis from our antenatal clinic. Patients with an Hb level between  $\geq 9.0$  g/dl and <10.0 g/dl received 200 mg (10 ml) iron sucrose (Venofer<sup>®</sup>, Vifor International, St. Gallen, Switzerland) intravenously twice weekly (group A). If response to therapy was poor (i.e., Hb increase <0.7 g/dl) after 2 weeks (4 infusions), patients additionally received 10,000 U rhEPO (Eprex<sup>®</sup>, Janssen-Cilag, Baar, Switzerland) (group B).

Patients with an Hb level <9.0 g/dl received iron sucrose (Venofer) and rhEPO (Eprex) twice weekly from the start of therapy (group C).

In all three groups therapy was continued for a maximum of 4 weeks (or 8 infusions, as after 1,600 mg iron infused a further increase in Hb was not to be expected) or until the target Hb level of 11.0 g/dl was reached or until delivery.

### Drug Administration

After inserting a butterfly into the cubital vein, 200 mg iron sucrose, diluted in 100 ml 0.9% saline solution, were infused over 10 min. The cannula was flushed again with 5 ml saline solution and if appropriate, rhEPO was then injected as a bolus (1 ml); injection was again followed by a saline solution flush. Heart rate and blood pressure were monitored before and 10 min after therapy.

### Laboratory Tests

Blood samples were taken twice weekly immediately before therapy (in ethylenediaminetetraacetic acid-treated tubes, Vacutainer<sup>™</sup>, Becton Dickinson, Plymouth, UK) for routine hematologic examination, including platelet count, and once weekly (serum samples) for determination of iron status [ferritin level, transferrin saturation, soluble transferrin receptor (sTfR), C-reactive protein level to detect underlying infection, and endogenous erythropoietin (eEPO) levels]. Hematologic parameters were determined using a flow cytometric hematology analyzer (Advia<sup>®</sup> 120, Bayer Health Care, Leverkusen, Germany).

Erythropoietin (EPO) level was measured by enzyme-linked immunosorbent assay (R&D Systems Europe, Abingdon, UK). For measuring serum ferritin, chemiluminometric sandwich immunoassay was performed using the Automated Chemiluminescence System (ACS) 180 (Chiron Diagnostics, East Walpole, Mass., USA). C-reactive protein (TinaQuant turbidimetric immunoassay, Roche Diagnostics, Rotkreuz, Switzerland) and serum iron (FerroZine method, Hach, Loveland, Colo., USA) were

**Table 1.** Baseline characteristics and pretreatment laboratory characteristics in groups A (iron sucrose), B (iron sucrose + rhEPO after 2 weeks) and C (iron sucrose + rhEPO from the beginning of therapy)

Parameter (reference range)	Group A (n = 27)	Group B (n = 32)	Group C (n = 25)	p
Gestational age, weeks	31.7 ± 6.5 (16–39)	28.8 ± 5.1 (16–37)	28.5 ± 7.1 (16–41)	n.s.
Hb concentration, g/dl (>11.0 <sup>a</sup> )	9.5 ± 0.3 (9.1–9.9)	9.5 ± 0.3 (9.0–9.9)	8.3 ± 0.4 (7.1–8.9)	<0.001 A, B vs. C
Hematocrit, % (>33 <sup>a</sup> )	29.3 ± 1.3 (26.9–32.0)	28.9 ± 1.5 (26.3–31.9)	26.8 ± 1.4 (24.8–29.0)	<0.001 A, B vs. C
Mean corpuscular volume, fl (80–100)	79.7 ± 6.8 (66.5–93.0)	82.8 ± 6.9 (69.2–93.9)	73.1 ± 6.7 (61.9–88.7)	<0.001 A, B vs. C
Mean corpuscular Hb, pg (26–34)	25.8 ± 2.9 (20.6–31.5)	27.3 ± 3.0 (21.3–31.5)	22.7 ± 3.0 (17.8–29.9)	<0.001 A, B vs. C
Mean corpuscular Hb concentration, g/dl (31–36)	32.4 ± 1.2 (29.7–34.0)	32.9 ± 1.3 (30.6–36.2)	30.9 ± 1.8 (27.7–33.7)	<0.001 A, B vs. C
Reticulocyte count, % (0–1.5)	2.6 ± 0.9 (1.2–5.6)	2.1 ± 0.9 (0.5–4.8)	2.3 ± 1.1 (1.1–5.5)	n.s.
Reticulocyte corpuscular Hb, pg (25–28)	27.8 ± 4.2 (21.5–38.0)	27.2 ± 3.3 (19.4–33.3)	24.3 ± 3.5 (18.4–32.8)	<0.001 A vs. C
Hypochromic red blood cell population, % (<2.5)	9.8 ± 9.3 (0.4–37.0)	6.8 ± 8.3 (0.1–32.2)	22.7 ± 16.0 (1.0–51.7)	<0.001 A, B vs. C
Microcytic red blood cell population, % (<2.5)	7.3 ± 8.4 (0.4–31.9)	4.9 ± 7.1 (0.2–30.3)	15.4 ± 11.7 (0.9–41.8)	<0.05 A vs. C
EPO concentration, U/l (<20)	69.3 ± 42.8 (21.4–173.0)	46.6 ± 29.8 (10.0–138.0)	87.3 ± 49.7 (20.0–191.0)	<0.001 B vs. C
Ferritin concentration, µg/l (15–150)	5.4 ± 2.3 (2.0–12.0)	7.8 ± 3.7 (3.0–15.0)	6.1 ± 3.7 (2.0–15.0)	<0.05 A vs. B
Transferrin saturation, % (>20)	9.2 ± 8.2 (2.4–40.1)	11.6 ± 7.4 (3.3–30.8)	6.3 ± 6.8 (2.0–32.3)	<0.05 B vs. C
sTfR concentration, µg/ml (2.2–5.0)	10.2 ± 4.3 (4.8–20.5)	8.4 ± 3.3 (2.4–16.1)	3.4 ± 4.8 (5.9–26.6)	<0.05 A vs. C
TfR-F index (<3.8)	16.1 ± 8.7 (5.9–42.9)	10.9 ± 5.7 (2.4–25.4)	21.5 ± 11.5 (5.1–52.9)	<0.001 B vs. C
Vitamin B <sub>12</sub> concentration, ng/l (180–900 <sup>b</sup> )	193.2 ± 50.3 (90.0–295.0)	243.4 ± 132.3 (82.0–710.0)	227.2 ± 87.4 (88.0–492.0)	n.s.
Red blood cell folate concentration, µg/l (>165)	361.4 ± 102.9 (165.0–618.0)	332.2 ± 164.8 (103.0–800.0)	336.7 ± 117.7 (205.0–707.0)	n.s.
C-reactive protein concentration, mg/l (<10)	4.5 ± 2.4 (2.0–9.0)	4.9 ± 2.5 (2.0–10.0)	3.9 ± 2.2 (2.0–10.0)	n.s.

Data given as mean ± SD, with ranges in parentheses. <sup>a</sup> Third trimester reference value. <sup>b</sup> Reference value for nonpregnant patients.

assayed using a Roche/Hitachi 747 (Roche Diagnostics, Englewood, N.J., USA) workstation; transferrin saturation and sTfR concentration were measured by enzyme immunoassay based upon the double antibody sandwich method (Ramco Laboratories, Houston, Tex., USA).

Erythrocyte folate and vitamin B<sub>12</sub> (chemiluminometric sandwich immunoassay, Beckman Coulter, Fullerton, Calif., USA) were also assessed before the start of therapy.

The ratio of sTfR and serum ferritin was calculated using the formula: sTfR at inclusion/log ferritin at inclusion.

#### Statistics

For intergroup comparisons nonparametric ANOVA with post hoc Bonferroni/Dunn analysis was performed (SatView 5.0.1, SAS Institute, Cary, N.C., USA). A significance level of <0.05 was used in all tests. Data are given as mean ± SD.

## Results

Eighty-four patients were included in this study. All patients were of Caucasian ethnicity. Fifty-nine patients (groups A and B) had a baseline Hb level between 9.0 and 9.9 g/dl, of whom 32 women responded poorly to the initial therapy, receiving additional rhEPO injections after

2 weeks of treatment. Twenty-five patients (group C) had a baseline Hb level below 9.0 g/dl. Baseline hematologic characteristics and iron parameters are given in table 1.

The groups did not differ statistically significantly in age or time of treatment initiation. No patient had an abnormal C-reactive protein level. The groups did not differ in vitamin B<sub>12</sub> or erythrocyte folate levels. However, some patients showed levels below the normal range for nonpregnant patients, but no macrocytosis or elevated percentage of macrocytics.

#### Hematologic Response

The target Hb level was 11.0 g/dl for all three groups. Therapy was stopped after the target Hb level was reached or after a maximum iron dose of 1,600 mg. The overall Hb level after therapy was 11.0 g/dl (±0.5, range 10.0–12.6 g/dl). Thirty-one patients had an Hb level between 10.0 and 10.9 g/dl, and 53 patients had an Hb level of 11.0 g/dl or higher. The mean duration of therapy was 3.5 weeks (7 infusions).

Patients with severe anemia, treated initially with a combination of iron sucrose and rhEPO, showed an immediate response to therapy (group C). The mean Hb lev-

el in this group after therapy was 11.2 g/dl ( $\pm 0.4$ , range 10.1–12.6 g/dl). Twenty patients had an Hb level  $\geq 11.0$  g/dl, 5 patients had an Hb level between 10.0 and 10.9 g/dl, of whom 1 patient was not able to complete therapy as she gave birth at term after the second infusion.

Patients with moderate anemia ( $9.0 \leq \text{Hb} < 10.0$  g/dl; groups A and B) were initially treated with iron sucrose alone twice weekly. Of the 59 patients, 32 responded poorly to therapy according to our protocol (Hb increase  $< 0.7$  g/dl within 14 days, i.e., after 4 infusions of 200 mg iron sucrose) and received additional rhEPO as therapy continued.

In the 27 patients responding well to therapy (group A), the mean Hb level after therapy was 11.1 g/dl ( $\pm 0.4$ , range 10.1–12.0 g/dl) after a mean duration of therapy of 2.5 weeks (5 infusions).

The remaining 32 patients (group B) had a mean post-treatment Hb level of 10.9 g/dl ( $\pm 0.4$ , range 10.0–11.7 g/dl) after a mean of 4 weeks of therapy (8 infusions).

Patients in group A presented statistically significantly higher Hb values compared to patients in group B from day 4 until day 22 of therapy (day 4,  $p = 0.005$ ; day 8,  $p < 0.0001$ ; day 11,  $p = 0.003$ ; day 15,  $p < 0.0001$ ; days 18 and 22,  $p = 0.005$ ) and also compared to patients in group C from day 4 until day 15 (days 4, 8, 11, and 15,  $p < 0.0001$ ). Hb value in group B was statistically significantly higher on days 4 and 8 compared to group C (day 4,  $p < 0.0001$ ; day 8,  $p < 0.005$ ). The course of Hb in all three groups during treatment is shown in figure 1.

Those patients identified as poor responders to intravenous iron therapy (group B) showed statistically significantly lower eEPO levels compared to patients of group A who had the same degree of anemia ( $46.6 \pm 29.8$  vs.  $69.3 \pm 42.8$  U/l;  $p < 0.05$ ). Furthermore, the transferrin receptor-ferritin index (TfR-F index) was statistically significantly lower in these patients compared to group A ( $10.9 \pm 5.7$  vs.  $16.1 \pm 8.7$ ;  $p < 0.05$ ). The index is calculated as sTfR at baseline/log serum ferritin at baseline, serving as an established tool for distinguishing iron deficiency anemia from anemia of inflammation. The ferritin level at baseline was also statistically significantly higher in those patients compared to group A ( $7.8 \pm 3.7$  vs.  $5.4 \pm 2.3$   $\mu\text{g/l}$ ;  $p < 0.05$ ).

#### Iron Status

Serum ferritin was measured once weekly for monitoring the patients' iron stores. Overall pretreatment ferritin was 6.4  $\mu\text{g/l}$  ( $\pm 3.7$ , range 2.0–15.0  $\mu\text{g/l}$ ). At the end of therapy, overall ferritin was 184.9  $\mu\text{g/l}$  ( $\pm 95.9$ , range 55.0–528.0  $\mu\text{g/l}$ ). Apart from the above-mentioned dif-

ference at baseline, there was no statistically significant difference in all three groups throughout the course of therapy, but a tendency to lower ferritin values was observed in those patients treated with rhEPO and iron sucrose from the beginning of therapy baseline (group C, Hb  $< 9.0$  g/dl) (fig. 2).

Transferrin saturation increased from overall baseline 9.2% ( $\pm 7.7$ , range 2.0–40.1%) to overall 19.6% ( $\pm 8.9$ , range 6.1–51.2%) at the end of therapy. At inclusion, transferrin saturation was significantly lower in group C compared to group B (table 1). There was no statistically significant difference between the three groups at the end of therapy.

sTfR was elevated in all three groups at baseline, with statistically significantly higher values in group C compared to the other two groups (table 1). This difference remained throughout the course of therapy (days 8 and 15: group C vs. group A,  $p = 0.001$ , group C vs. group B,  $p < 0.0001$ ; day 22: group C vs. group A,  $p < 0.001$ , group C vs. group B,  $p < 0.001$ ) (fig. 2).

Hypochromic red cells showed a comparable course, with statistically significantly higher values in group C at baseline (table 1). Hypochromic red cells remained statistically significantly elevated during therapy in this group (days 8, 11 and 15: group C vs. group A and group B,  $p < 0.0001$ ; day 18: group C vs. group A,  $p < 0.05$ , group C vs. group B,  $p < 0.001$ ; day 22: group C vs. group A,  $p < 0.05$ , group C vs. group B,  $p = 0.001$ ; day 25: group C vs. group B,  $p < 0.05$ ; data available from author upon request).

eEPO levels showed a statistically significant difference as shown in table 1. After 1 week of therapy, eEPO levels declined but remained elevated until the end of therapy (with no statistically significant difference observed between the three groups throughout therapy). Overall the mean eEPO level at the end of therapy was 28.3 U/l ( $\pm 17.0$ , range 13.0–90.4 U/l).

#### Safety

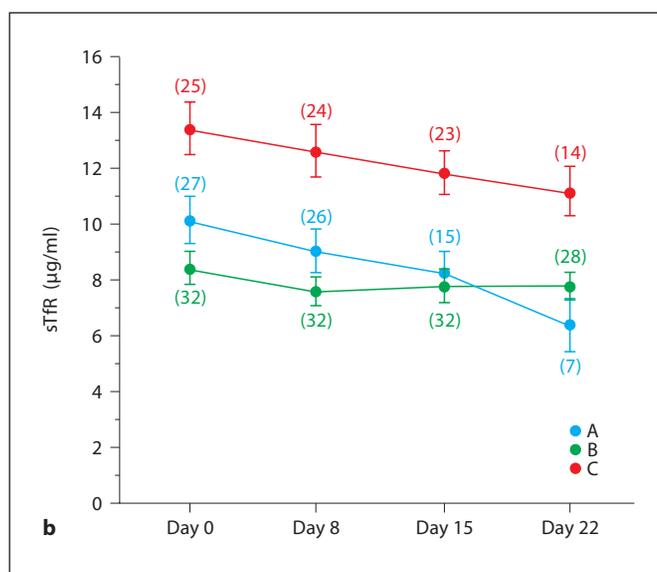
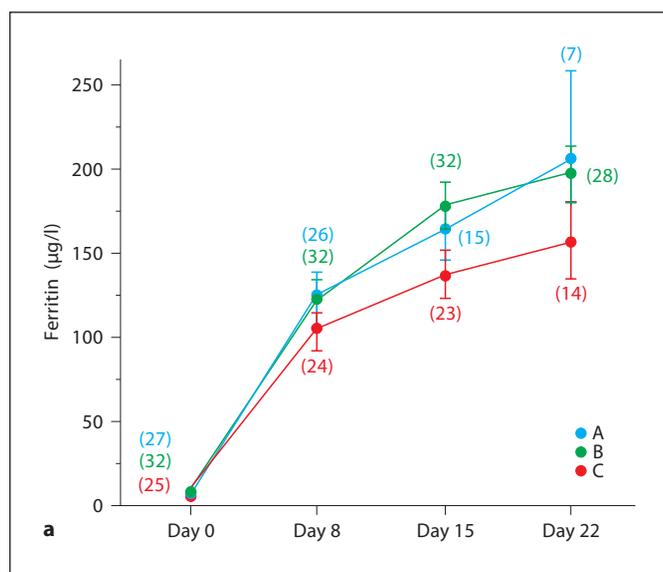
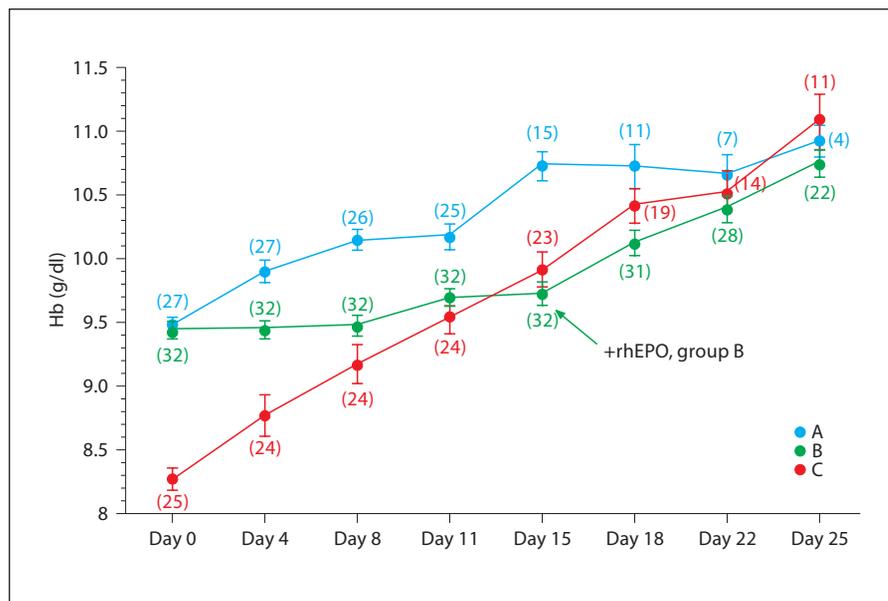
There were no serious adverse events in all three groups. No hypotensive responses, allergic reactions, or thromboembolic complications were seen during therapy. Most patients reported a metallic taste during iron sucrose infusion.

#### Maternal and Fetal Outcomes

Mean gestational age at delivery was  $39.7 \pm 3.1$  weeks, and mean birth weight was  $3,370 \pm 590$  g. There was no statistically significant difference between all three groups. Clinical parameters were normal in all neonates.

None of the patients needed antepartum or postpartum blood transfusions.

**Fig. 1.** Course of Hb during therapy (group A: intravenous iron sucrose twice weekly; group B: intravenous iron sucrose twice weekly and additional intravenous rhEPO twice weekly after 2 weeks of treatment; group C: iron sucrose and rhEPO intravenously twice weekly). Numbers in parentheses indicate number of patients at each time point.



**Fig. 2.** Course of ferritin values (a) and sTfR values (b) during the course of the different treatment regimens. Numbers in parentheses indicate number of patients at each time point.

## Discussion

The present study shows an effective treatment regimen using iron sucrose alone or in combination with rhEPO for patients with various degrees of iron deficiency anemia in pregnancy. It has to be pointed out that all patients developed anemia despite routine prescription of

oral iron supplements (80 mg per day) from the beginning of the second trimester. Patients with severe anemia treated with the combination of rhEPO and iron sucrose show a rapid response as indicated by the increases in Hb and reticulocyte count (data not shown). It is well known that rhEPO therapy delivers optimal results when combined with an effective iron substitution to avoid or at

least diminish functional iron deficiency. Especially when iron stores are empty before therapy, only parenterally administered iron (i.e., iron sucrose) is able to optimize therapy [12, 13]. In our patients functional iron deficiency was already present at the start of therapy and did not worsen during the observation period. Due to the fact that in those patients treated with rhEPO and iron sucrose functional iron deficiency was still present at the end of therapy (shown by elevated hypochromic red cells; data available upon request), the question arises whether these patients are eligible for oral iron treatment after the end of therapy.

In patients with moderate iron deficiency anemia treated with iron sucrose alone we observed variable response. One aim of our study protocol was to discriminate so-called 'nonresponders' from patients with moderate anemia who show a good response to intravenous iron sucrose. To identify those patients who might benefit from an additional rhEPO therapy, we set a cutoff at an Hb increase of  $<0.7$  g/dl after 4 infusions of 200 mg iron sucrose each within 14 days. This cutoff was chosen on the basis of data on optimal response to oral iron therapy in other clinical settings. With an oral dose of 105 mg/day optimal Hb increase was given as approximately 0.1 g/dl/day [14]. For a conservative anticipation we cut this number by half. Those patients receiving additional rhEPO in the consecutive therapy sessions (group B) had statistically significantly lower rhEPO levels at baseline compared to patients of group A who had the same degree of anemia. There are no reference values for eEPO levels in pregnancy, but Cazzola et al. [15] suggested that eEPO levels  $<100$  U/l are disproportionately low for anemia. Furthermore, there was a statistically significantly lower ferritin level in group A compared to group B, although both baseline ferritin mean values were well below 10  $\mu$ g/l. sTfR concentration was not statistically significantly different in both groups, but when the sTfR/log ferritin ratio was calculated, the so-called nonresponders (group B) showed statistically significantly lower values compared to the other two groups. The TfR-F index is used to distinguish iron deficiency anemia from anemia of inflammation and represents a combination of measurements of iron stores (ferritin) and functional tissue iron (sTfR) [16]. In our study population, iron deficiency anemia was proven by pathologically low ferritin values. A few patients in group B had normal hemoglobinization (normal reticulocyte hemoglobin content and normal TfR-F index) despite having iron deficiency anemia according to their Hb and ferritin levels. One could speculate that in a subgroup of our investigated population,

there exists a form of anemia comparable to anemia of inflammation (or anemia of chronic disease), i.e., supplemented iron is diverged from the circulation into storage sites of the reticuloendothelial system and proliferation of erythroid progenitor cells is impaired [17]. As in our patients inflammation/infection was clinically excluded, subtle changes in the mechanisms of iron household possibly influence the success of intravenous iron therapy. As hepcidin was identified as the long-sought iron-regulatory hormone [18], a validated assay in blood or urine of those anemic patients would provide a starting point for further investigation into the variable efficacy of intravenous iron therapy. Interestingly, only after 2 injections of rhEPO did the women in group B (nonresponders) reach comparable Hb concentrations as the women in group A at the same point of time in therapy. This would support the theory of blunted eEPO production (comparable to diminished EPO release in anemia of inflammation) in the group of the so-called nonresponders.

It is also conceivable that these patients already profited from previous oral iron therapy as a lower TfR-F index reflects lower body iron demand.

Another explanation might lie in the fact of considerable variations in the degree of hemodilution in pregnant women. According to a publication of Milman [19], the Hb concentration may vary up to 3.5 g/dl. It is known that Hb as a single parameter is not valid for estimation of the iron status. If one has a closer look at the baseline laboratory parameters of the patients of the group successfully treated with iron alone (group A) and the so-called nonresponders (group B), it is evident that for the same degree of anemia (shown in Hb concentration and hematocrit) group B has a statistically significantly higher serum ferritin concentration and a statistically significantly lower eEPO concentration compared to group A. Mean corpuscular volume, mean corpuscular Hb and transferrin saturation also show a tendency towards higher values, although not statistically significant.

To date, nonresponders to intravenous iron therapy have not been described, but in the study of Bayoumeu et al. [6], for instance, regarding the increase in Hb, no difference between orally and intravenously administered iron was found. In this study, the total iron sucrose dose to be administered was calculated using the formula:  $\text{weight} \times (\text{target Hb} - \text{actual Hb}) \times 0.24 + 500$  mg, as provided by the manufacturer of Venofer [20]. Unsurprisingly, only iron sucrose appeared to restore iron stores with a statistically significant difference at any time of the treatment period compared to oral iron [6]. The above-mentioned nonresponders to intravenous iron

might explain the lack of benefit regarding Hb increase of intravenous iron compared to oral iron in the study by Bayoumeu et al. [6].

Similar to our experience published in previous studies [5, 21], the safety profile of iron sucrose (Venofer) alone or in combination with rhEPO (Eprex) was favorable. There were no serious adverse events in all three groups. No hypotensive responses, allergic reactions, or thromboembolic complications were seen during therapy. Most patients reported a metallic taste during iron sucrose infusion.

In conclusion, iron sucrose given intravenously is a safe option for the treatment of iron deficiency anemia in pregnancy, avoiding well-known side effects of high-dose oral iron supplementation, i.e., constipation or abdominal pain. In cases of severe iron deficiency anemia even a combination with rhEPO might be considered, especially if further risk factors are noted, such as placenta previa, or being a member of Jehovah's witnesses. If a patient is not responding well to therapy with iron sucrose alone, additional treatment with rhEPO might be considered.

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