

# Efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of resistant iron-deficiency anemia during pregnancy

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**OBJECTIVE:** This study was undertaken to determine the efficacy and safety of intravenously administered iron sucrose with versus without adjuvant recombinant human erythropoietin in the treatment of gestational iron-deficiency anemia resistant to therapy with orally administered iron alone.

**STUDY DESIGN:** Forty patients with gestational iron-deficiency anemia were randomly assigned to receive intravenously iron sucrose plus recombinant human erythropoietin or iron sucrose alone twice weekly. Target hemoglobin value was 11.0 g/dL. Efficacy measures were reticulocyte count, increase in hematocrit, and time to target hemoglobin level (treatment duration in weeks and need for continued therapy after 4 weeks).

**RESULTS:** Both regimens were effective, but with adjuvant recombinant human erythropoietin the reticulocyte counts were higher from day 4 ( $P < .01$ ), increases in hematocrit were greater from day 11 ( $P < .01$ ), and the median duration of therapy was shorter (18 vs 25 days), with more patients reaching the target hemoglobin level by 4 weeks of treatment ( $n = 19$  vs  $n = 15$ ). The groups did not differ with respect to maternal-fetal safety parameters.

**CONCLUSION:** Adjuvant recombinant human erythropoietin safely enhanced the efficacy of iron sucrose in the treatment of gestational iron-deficiency anemia resistant to orally administered iron alone. (Am J Obstet Gynecol 2001;184:662-7.)

**Key words:** Erythropoietin levels, gestational anemia, iron-deficiency anemia, iron sucrose, recombinant human erythropoietin

Iron-deficiency anemia is one of the most common and best recognized problems in pregnancy. In severe cases, with the attendant threat of increased maternal-fetal morbidity and mortality, safe and effective treatment is mandatory. Traditional therapy, which is based on either oral administration of iron or blood transfusion, or both, has had drawbacks: the efficacy of orally administered high-dose iron was limited by the high incidence of side effects and thus noncompliance, whereas blood transfusion remains a last resort because of patient choice and the risks of infection, immunologic impact, and transfusion reactions.<sup>1, 2</sup>

Modern alternative strategies call for parenteral administration of new, well-tolerated iron preparations, (eg, iron sucrose) together with recombinant human erythropoietin (rhEPO), which has been used successfully in the

treatment of postpartum anemia<sup>1, 3-5</sup> and increasingly during pregnancy,<sup>1, 6, 7</sup> in which setting it has been shown to be safe and not to cross the placenta.<sup>6, 8-10</sup> We have already published pilot studies of rhEPO in the treatment of gestational anemia, including when complicated by heterozygous  $\beta$ -thalassemia.<sup>11, 12</sup> We now report a randomized comparison of parenterally administered iron sucrose with versus without adjuvant rhEPO in the treatment of severe gestational iron-deficiency anemia.

## Patients and methods

The hospital institutional review board approved the study protocol, and patients gave informed consent before inclusion. Treatment was not started before 21 weeks' gestation and was continued for 4 weeks or until the target hemoglobin level of 11.0 g/dL was reached.

**Inclusion criterion.** Subjects had progressive iron-deficiency anemia, considered to be a hemoglobin level  $<10.0$  g/dL according to the Centers for Disease Control and Prevention<sup>13</sup> criteria for pregnancy anemia (10.5 g/dL, 5th percentile in the second trimester; 11.0 g/dL, 5th percentile in the third trimester) and a ferritin level  $<15$   $\mu$ g/L. All patients received orally administered iron sulfate (80 mg twice daily) for  $\geq 2$  weeks before starting

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the study therapy. Random assignment was initiated when the hemoglobin dropped to <10.0 g/dL despite orally administered iron supplementation.

**Exclusion criteria.** Women with anemia from causes other than iron deficiency (eg, vitamin B<sub>12</sub> or folate deficiency, infection, chronic bleeding, or renal failure) previous blood transfusions, history of iron intolerance, or with history of hematologic disease (eg, thalassemia or sickle cell disease) were all excluded.

**Study groups.** All patients were recruited on a consecutive and prospective basis from our antenatal clinic. Hemoglobin level and red blood cell parameters were determined at presentation. Patients with a hemoglobin level <10.5 g/dL received orally administered iron sulfate (80 mg twice daily) regardless of whether they had used iron tablets previously. They were instructed to take the tablets on an empty stomach 1 hour before meals and were informed about the necessity to take them regularly. Hemoglobin level was redetermined after 2 weeks, and the patient was included if the level had dropped to or remained <10.0 g/dL. Compliance was assessed before study entry by direct questioning regarding the regularity of tablet use during the preceding 2 weeks.

Forty patients were randomly assigned to 2 treatment groups of 20 patients each by means of a computer-generated list: Group 1 received rhEPO (Eprex; Janssen-Cilag AG, Schaffhausen, Switzerland) at 300 U/kg body weight plus iron sucrose (Venofer; Vifor AG, St Gallen, Switzerland) at 200 mg (10 mL) intravenously administered twice weekly 72 to 96 hours apart; group 2 received iron sucrose (Venofer) alone, with the same dose, administration route, and schedule as in group 1.

**Drug administration.** A butterfly cannula was inserted into a forearm vein, and its position was confirmed by flushing with 5 mL saline solution and aspirating blood. A 1-mL test dose of iron sucrose (10 mg) at room temperature was then injected while the patient was observed and asked about side effects for 2 to 3 minutes. In the absence of abnormal reaction, the remainder of the dose (9 mL; 90 mg) was injected during the course of 10 minutes, and the cannula was flushed again with 5 mL saline solution. In group 1 rhEPO was then injected as a bolus (approximately 2 mL); injection was again followed by a saline solution flush. Heart rate and blood pressure were monitored before and again 10 minutes after therapy.

**Laboratory tests.** Blood samples were taken twice weekly (in ethylenediaminetetraacetic acid–treated tubes) for routine hematologic examination, including platelet count, and once weekly (serum samples) for determination of iron status (ferritin level, transferrin saturation, hypochromic red blood cell count as a marker of functional iron deficiency, C-reactive protein level to detect underlying infection affecting the hematologic response, and endogenous erythropoietin levels). All parameters were measured immediately after sampling.

Hematologic parameters were measured by AutoAnalyzer (Technicon H\*3; Bayer AG, Leverkusen, Germany), erythropoietin level was measured by radioimmunoassay (EPO-Trac; DiaSorin Inc, Stillwater, Minn), ferritin was determined by immunochemiluminescence, and C-reactive protein was evaluated by immunoprecipitation. Vitamin B<sub>12</sub> and erythrocyte folate levels were measured once before therapy by radioimmunoassay.

**End points.** Hematologic response was measured by the increases in hematocrit and reticulocyte count.

**Statistics.** Data are given as the mean ± SD. Groups were compared with the StatView version 4.5 for Macintosh (SAS Institute, Inc, Cary, NC) statistical package. Nonparametric Mann-Whitney tests were used, and significance was accepted at  $P < .05$ .

## Results

**Baseline patient characteristics.** Thirty of 40 patients reported having used iron tablets since early pregnancy (from the antenatal booking), 5 had received supplemental iron after several blood tests, and 5 had never used iron supplements before. Seven patients had a history of anemia, including blood transfusion (1/7), intrauterine growth restriction (3/7), and intrauterine death (1/7). All patients reported regular use of iron tablets for 2 weeks before study entry. Before treatment, iron-deficiency anemia (ferritin <15 µg/L) was confirmed in all patients.

The groups did not differ in baseline hematologic characteristics, iron status, or time of treatment initiation (approximately 32 weeks' gestation; Table 1). Apart from asymptomatic urinary tract infection ( $n = 5$ ), no patient had clinical evidence of infection or an abnormal C-reactive protein level. Vitamin B<sub>12</sub> and erythrocyte folate levels were also normal.

**Hematologic response.** Both groups showed an immediate reticulocyte response and continuous increase in hematocrit. Group 1 (with rhEPO) had higher reticulocyte counts than group 2 from day 4 (Fig 1, A) of treatment and had greater increases in hematocrit from day 11 (Fig 1, B), paralleled by a consistently greater decrease in endogenous erythropoietin level (Fig 1, C). Endogenous erythropoietin level was elevated before treatment, but this did not correlate with either hemoglobin level ( $R^2 = 0.007$ ; data not shown) or hematocrit ( $R^2 = 0.003$ ). In 25 of 40 patients the endogenous erythropoietin level (<100 U/L) was disproportionately low for the observed grade of anemia.<sup>14</sup>

Median durations of therapy were 18 days in group 1 and 25 days in group 2. After 4 weeks only 1 patient in group 1 had not reached the target hemoglobin level of 11.0 g/dL, whereas 5 patients in group 2 had not done so, with hemoglobin values ranging from 9.9 to 10.6 g/dL.

**Iron status.** Ferritin level (Fig 2, A) and transferrin saturation (Fig 2, B) increased continuously until the end of therapy. Both sets of values were normal in all patients, with no significant difference between the groups.

**Table I.** Gestational ages at treatment initiation and pretreatment laboratory characteristics in groups 1 and 2

	Group 1 (rhEPO plus iron sucrose)	Group 2 (iron sucrose alone)	Reference range
Gestational age (wk)			
Mean $\pm$ SD	31.6 $\pm$ 5.1	31.7 $\pm$ 4.9	
Range	22-38	20-38	
Hemoglobin concentration (g/dL)			
Mean $\pm$ SD	9.0 $\pm$ 0.7	9.2 $\pm$ 0.6	
Range	7.9-9.9	8.2-9.9	>10.5*
Hematocrit (%)			
Mean $\pm$ SD	28.4 $\pm$ 2.4	29.3 $\pm$ 1.9	
Range	24.8-32.5	25.5-32.8	>32*
Mean corpuscular volume (fL)			
Mean $\pm$ SD	80.6 $\pm$ 8.2	79.2 $\pm$ 5.6	
Range	62.1-95.3	71.2-90.3	80-100
Reticulocyte count (%)			
Mean $\pm$ SD	1.9 $\pm$ 1.3	1.8 $\pm$ 0.6	
Range	0.3-7.0	0.8-3.0	0-1.5
Erythropoietin concentration (U/L)			
Mean $\pm$ SD	75.9 $\pm$ 51.6	85.5 $\pm$ 61.0	
Range	12.7-207.7	22.9-193.0	<20
Transferrin saturation (%)			
Mean $\pm$ SD	9.2 $\pm$ 8.0	6.1 $\pm$ 3.7	
Range	2.0-33.3	2.3-18.6	>20
Ferritin concentration ( $\mu$ g/L)			
Mean $\pm$ SD	7.5 $\pm$ 4.8	7.1 $\pm$ 4.3	
Range	2.0-15.0	2.0-15.0	15-150
Hypochromic red blood cell proportion (%)			
Mean $\pm$ SD	14.5 $\pm$ 12.6	18.2 $\pm$ 10.3	
Range	1.0-46.1	3.6-39.9	<2.5
Vitamin B <sub>12</sub> concentration (ng/L)			
Mean $\pm$ SD	193.5 $\pm$ 125.4	199.4 $\pm$ 125.7	
Range	61.1-540.0	72.0-473.0	180-900
Red blood cell folate concentration ( $\mu$ g/L)			
Mean $\pm$ SD	417.4 $\pm$ 152.6	365.1 $\pm$ 147.8	
Range	181.0-729.0	152.0-669.0	>165
C-reactive protein concentration (mg/L)			
Mean $\pm$ SD	4.3 $\pm$ 2.1	4.6 $\pm$ 2.5	
Range	3.0-10.0	3.0-11.0	<10

No significant difference in any parameter according to Mann-Whitney test.

\*Second-trimester reference value.

Hypochromic red blood cell count (Fig 2, C) remained elevated from before treatment until the end of treatment, differing between the groups on days 18 and 21 because of a grossly elevated value in group 1 on each occasion (54% and 64%, respectively). Mean corpuscular volume increased in both groups and was higher in group 1 than in group 2 at the end of therapy (91.1  $\pm$  4.3 vs 84.8  $\pm$  6.3 fL;  $P < .05$ ).

**Safety.** There were no serious reactions to rhEPO or iron sucrose. Three patients reported a metallic taste, and 2 reported feeling warm for a few minutes. No hypotensive or hypertensive responses were seen during or after therapy.

No thromboembolic complications were seen. Platelet counts increased in all patients during correction of anemia but remained in the upper normal range in both groups. Mean maximal platelet counts ( $10^3$  cells/L) were 274.8  $\pm$  57.7  $\times 10^3$  cells/L in group 1 and 220.1  $\pm$  15.1  $\times 10^3$  cells/L in group 2. White blood cell counts and C-reactive protein levels were normal in both groups throughout the study period.

**Maternal and fetal outcomes.** Pretreatment maternal morbidities comprised tiredness (11/40), frequent nausea (10/40), premature contractions (8/40), orthostatic dysfunction (dizziness; 5/40), urinary tract infection (5/40), and frequent headaches (4/40), all of which improved in response to therapy. Mean blood pressure increased from 73.3 mm Hg (range, 50.6-98.3 mm Hg) at diagnosis to 76.0 mm Hg (range, 62.0-96.6 mm Hg) at the end of therapy ( $P = .01$ ). Ultrasonography detected intrauterine growth restriction and placental insufficiency in 2 of 40 patients. Mean gestational age at delivery was 40.0  $\pm$  1.2 weeks, and mean birth weight was 3399  $\pm$  407 g. All women had normal antepartum hemoglobin levels (>11.0 g/dL).

None of the women needed additional antepartum or postpartum blood transfusion. Clinical parameters and red blood cell index values were normal in all neonates.

#### Comment

This study shows that iron sucrose plus rhEPO was more effective in correcting pregnancy anemia than was

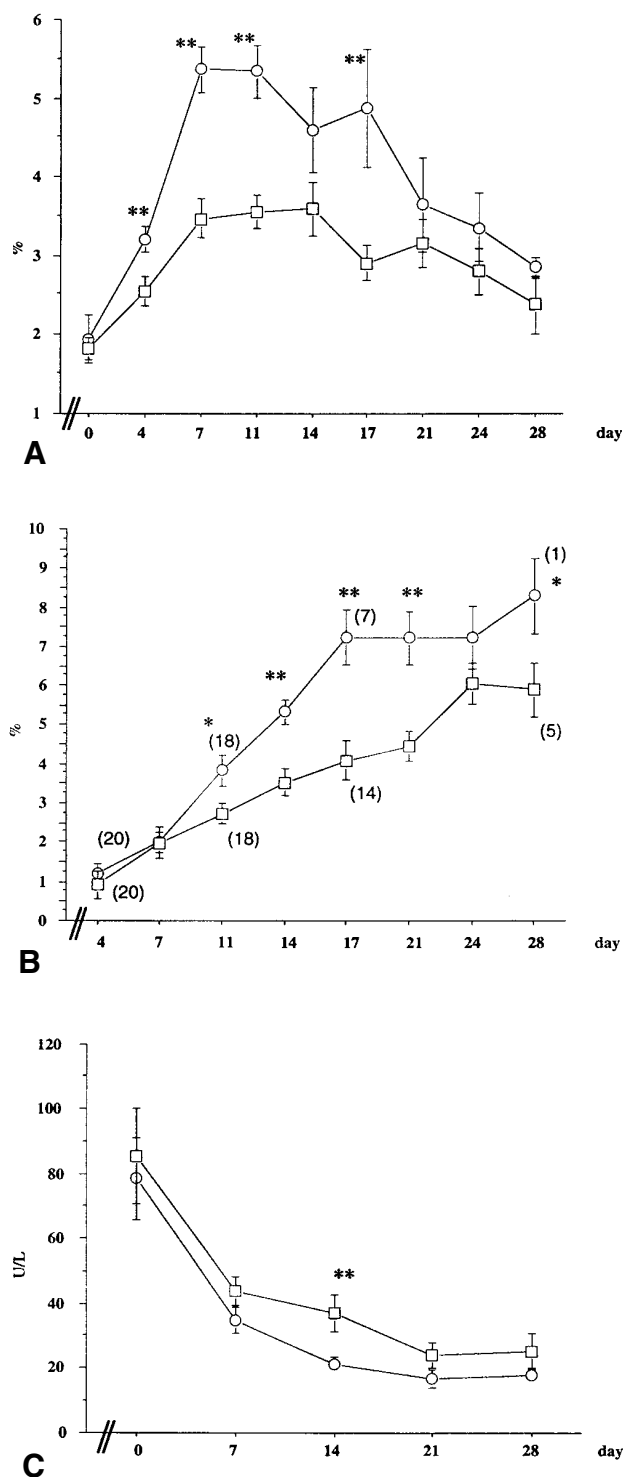
iron sucrose alone, as estimated by the increases in reticulocyte count, hematocrit, and hemoglobin level. Patients who received rhEPO reached the target hemoglobin level earlier. Iron sucrose alone was also effective, however, bringing into question the clinical relevance of the statistically significant differences between the groups. Several recent studies have described the utility of rhEPO in the treatment of nonrenal obstetric anemia.<sup>1, 5-7, 15</sup> We ourselves previously showed in a nonrandomized pilot study that rhEPO is an effective treatment for gestational iron-deficiency anemia.<sup>11</sup>

Because parenterally administered iron sucrose is also safe and effective, the combination of the 2 substances increases the efficacy of anemia therapy by stimulating erythropoiesis (rhEPO) at the same time that it delivers enough iron for hemoglobin synthesis and iron stores (iron sucrose).<sup>16, 17</sup> Indeed, it is now generally accepted that rhEPO should be combined with parenterally administered iron, especially when iron stores are empty before therapy. In our patients functional iron deficiency was already present before therapy, and it did not worsen during the observation period. The fact that functional deficiency was still present at the end of therapy, however, shows that iron must be supplemented until the end of pregnancy in patients such as ours with empty iron stores.

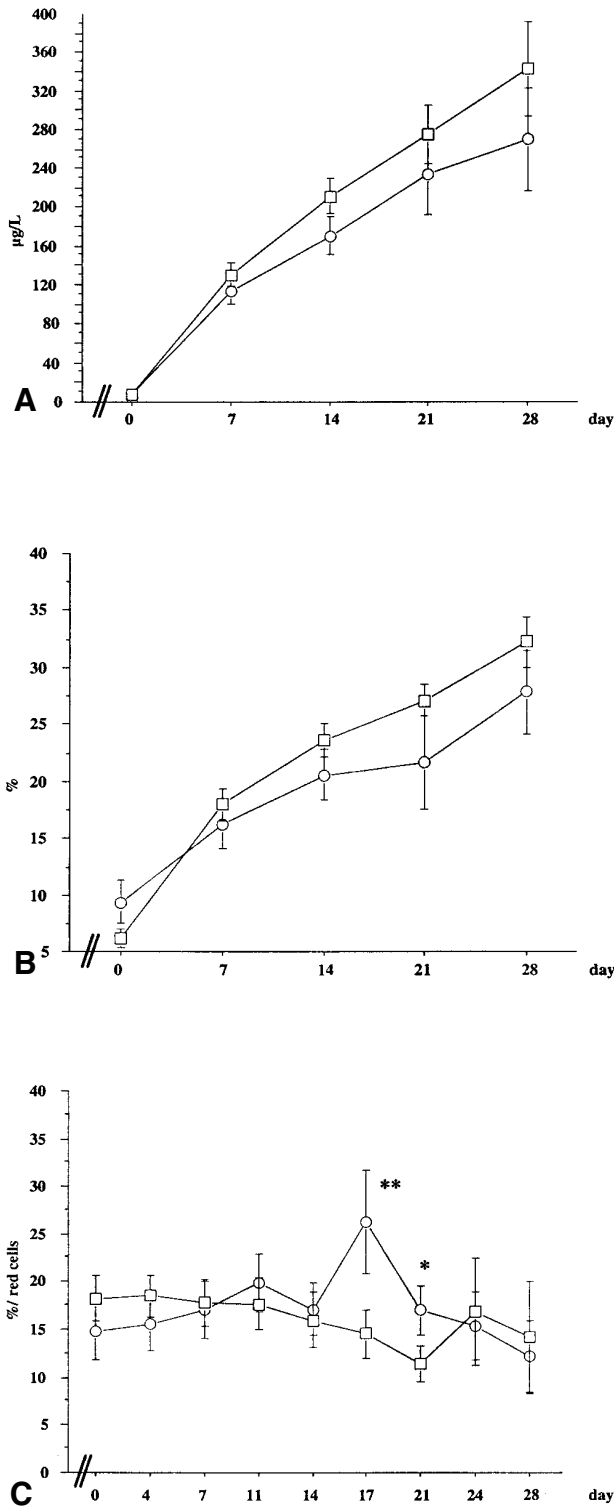
Future studies must seek to discriminate the patients most likely to benefit from rhEPO. There is already evidence that they include those with endogenous erythropoietin levels that are lower than proportional to the grade of anemia. Cazzola et al<sup>14</sup> have suggested that endogenous erythropoietin levels <100 U/L are disproportionately low for anemia and that such patients should therefore receive erythropoietin supplementation.

On the other hand, there are no reference values for anemia-related endogenous erythropoietin levels during pregnancy. The erythropoietin secretory response to anemia may differ between pregnant and nonpregnant states, and erythropoietin levels are dependent on various obstetric conditions, as shown previously by Goldstein et al.<sup>18</sup> Our study showed no correlation between endogenous erythropoietin level and hematocrit. This finding agrees with previous observations by Beguin et al<sup>19</sup> and Fuchs et al,<sup>20</sup> who suggested that erythropoietin secretion is blunted in pregnancy, possibly by inhibitory cytokines such as interleukin 1, interleukin 6, or interferon  $\gamma$ . Levels of these cytokines are elevated in pregnancy by activated immune mechanisms, and they inhibit erythropoietin secretion in vivo and in vitro.<sup>14</sup> In our patients we did not measure inflammatory cytokine levels but only C-reactive protein levels, which were in the normal range. However, we have preliminary data indicating that immune system activation interferes with iron metabolism and possibly with erythropoietin secretion, resulting in blunted erythropoiesis during pregnancy.<sup>21</sup>

Use of rhEPO might be limited to severe or complicated anemia or cases requiring rapid reconstitution of



**Fig 1.** Reticulocyte counts (A), increases in hematocrit versus day 0 (before treatment) (B), and decreases in endogenous erythropoietin levels versus day 0 (C) in pregnant patients with anemia receiving rhEPO plus iron sucrose (open circles) or iron sucrose alone (open squares). 1 Asterisk,  $P < .05$ , Mann-Whitney test; 2 asterisks,  $P < .01$ , Mann-Whitney test. Data points, Mean; error bars, SD. Numbers in brackets, Remaining patients per group with hemoglobin level <11.0 g/dL at each time point.



**Fig 2.** Iron status expressed as serum ferritin levels (A), transferrin saturations (B), and hypochromic red blood cell counts (C) in pregnant patients with anemia receiving rhEPO plus iron sucrose (open circles) or iron sucrose alone (open squares). 1 Asterisk,  $P < .05$ , Mann-Whitney test; 2 asterisks,  $P < .01$ , Mann-Whitney test. Data points, Mean; error bars, SD.

the red blood cell pool, such as women with placenta previa,<sup>22</sup> Jehovah's Witnesses with anemia,<sup>1, 6</sup> or special subgroups such as those with thalassemia or sickle cell disease.<sup>12, 15, 23</sup> Use of rhEPO could also serve as a second-line therapy if iron alone fails to increase the hematocrit within a defined interval. Because blood transfusions are a last resort, alternative strategies such as rhEPO plus parenterally administered iron are of considerable interest. The current literature proposes the following obstetric indications for rhEPO: erythropoietin-deficient anemia,<sup>3, 7</sup> severe or progressing iron-deficiency anemia,<sup>1, 6, 11</sup> Jehovah's Witness or other refusal of blood transfusion,<sup>1, 6, 14</sup> placenta previa (or placenta accreta),<sup>22</sup> preoperative and postoperative patients,<sup>1, 3, 5, 6</sup> autologous blood donation,<sup>1, 14, 16</sup> and hemoglobinopathy (eg, thalassemia and sickle cell disease).<sup>12, 15, 23</sup>

Recently al-Momen et al<sup>24</sup> compared intravenously administered iron sucrose complex with orally administered iron for the treatment of gestational iron-deficiency anemia: The mean treatment durations were 6.9 weeks and 14.9 weeks, respectively. Our data show that adjuvant rhEPO combined with an optimized dosage schedule shortens treatment considerably while avoiding the gastrointestinal side effects and associated poor compliance found in as many as 30% of patients receiving oral therapy.<sup>24</sup>

The cost of rhEPO means that its use is largely investigational and its indications are limited. In our study the mean duration of therapy was 15 days with rhEPO, versus 22 days without. In the Swiss health care setting the approximate drug costs are US \$1020 for iron sucrose plus rhEPO for 2 weeks versus US \$120 for iron sucrose alone for 3 to 4 weeks and US \$144 for orally administered iron sulfate at 160 mg/d for as long as 14 weeks (therapy plus restoration of iron stores, assuming a positive response). Antepartum blood transfusion costs US \$360 to US \$480 for 2 to 4 units.

The annual saving in combined antiviral therapy through the avoidance of human immunodeficiency virus and hepatitis B and C transmission through contaminated blood transfusion is US \$36,000 per case. It is difficult to predict the saving achieved through rapid and effective anemia reversal with rhEPO and consequent avoidance of blood transfusion for high peripartum blood loss, but we believe that in many cases the overall cost differs little, if at all, from that of ineffective treatment for antepartum anemia. Despite severe anemia at diagnosis, all the patients in our study were delivered at term, with no small-for-gestational-age infants and no blood transfusion requirements. This could be adduced as evidence of optimal treatment.

We conclude that iron sucrose plus rhEPO is the most effective treatment for pregnancy anemia, probably because of synergy, with rhEPO substituting for deficient endogenous erythropoietin to stimulate erythropoiesis and iron sucrose most effectively delivering iron for hemoglobin synthesis. The addition of rhEPO enhances the effi-

cacy of iron sucrose alone. The efficacy and safety of rhEPO during pregnancy warrant further evaluation, including in cases of nonrenal anemia. In addition, possible positive side effects such as the accumulation of rhEPO in maternal milk could be factored into the treatment equation in the future.<sup>25</sup>

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