Intravenous Ferric Carboxymaltose Compared With Oral Iron in the Treatment of Postpartum Anemia

A Randomized Controlled Trial

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OBJECTIVE: To estimate efficacy of rapid, large-dose intravenous (IV) administration of ferric carboxymaltose compared with oral iron therapy in anemic postpartum women.

METHODS: In a randomized, controlled trial, we assigned anemic women (hemoglobin [Hb] less than or equal to 10 g/dL) within 10 days postpartum to receive either IV ferric carboxymaltose (less than or equal to1,000 mg over 15 minutes, repeated weekly to achieve a total calculated replacement dose) or ferrous sulfate ($FeSO_4$) 325 mg orally thrice daily for 6 weeks.

RESULTS: One hundred seventy-four patients received 350 IV doses of ferric carboxymaltose (mean total dose 1,403.1 mg) in 3, 2, or 1 injection (10.9%, 79.3%, or 9.8% of patients, respectively); 178 received $FeSO_4$. Patients assigned to IV ferric carboxymaltose compared with those assigned to oral iron achieved a Hb rise greater than or equal to 2.0 g/dL earlier (7.0 compared with 14.0 days, $P<.001$), were more likely to achieve a Hb rise greater than or equal to 3.0 g/dL at any time (86.3% compared with 60.4%, $P<.001$), and were more likely to achieve a Hb greater than 12.0 g/dL (90.5% compared with 68.6%, $P<.001$). A similar proportion of patients achieved a Hb rise greater than or equal to 2.0 g/dL (96.4% compared with 94.1%, IV compared with oral, $P=.443$). There were no serious adverse drug reactions.

CONCLUSION: Large-dose IV ferric carboxymaltose administration is a new iron agent that is effective for the treatment of postpartum anemia. When compared with oral ferrous sulfate, IV ferric carboxymaltose is better tolerated, prompts a more rapid Hb response, and corrects anemia more reliably.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00396292

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LEVEL OF EVIDENCE: I

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Dr. Van Wyck is a consultant and serves as a speaker for American Regent Inc, a division of Luitpold Pharmaceuticals, Shirley, NY. He is also an investigator for a grant supported by American Regent Inc, and serves on the speaker's bureaus for Amgen, Thousand Oaks, CA, and Ortho Biotech, Bridgewater, NJ. Dr. Martens, Dr. Baker, and Dr. Seid have served as research investigators for Luitpold Pharmaceuticals. Dr. Martens and Dr. Seid also serve on the American Regent speaker's bureau. Dr. Mangione is an employee of Luitpold Pharmaceuticals.

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Postpartum anemia arises frequently,[1] affects low-income and minority women disproportionately,[1] imposes a substantial disease burden during a critical period of maternal–infant interaction,[2] and may give rise to lasting developmental deficits in infants of affected mothers.[3] Twenty-one percent of low-income women with a normal hemoglobin in the third trimester of pregnancy present with evidence of anemia at their first postpartum visit.[1] As many as 40% of Hispanic women and 48% of non-Hispanic African-American women are afflicted.[1] Postpartum anemia adversely affects maternal mood, cognition, and behavior and disrupts maternal–infant interactions.[2] Infants of mothers who are anemic at 10 weeks postpartum show evidence of development delay; moreover, these early deficits in infants are not reversed by subsequent successful treatment of maternal anemia.[3]

Iron deficiency is the most common cause of anemia in the postpartum period.[4] Although iron therapy is indicated in the anemic patient, both oral iron agents and currently available intravenous (IV) iron agents pose difficult challenges to effective iron replacement. Efficacy of oral iron is limited by gastrointestinal (GI) complaints and patient nonadherence,[3–5] whereas treatment with IV iron either risks anaphylaxis when using iron dextran[5] or requires multiple injections of low doses when using previously available non–dextran-containing agents.[6,7]

Ferric carboxymaltose complex is a non–dextran-containing investigational IV iron agent designed to be administered in large doses by rapid IV injection. The ability to safely inject a single dose as large as 1,000 mg in as little as 15 minutes and thereby reduce the need for multiple IV iron infusions renders this novel agent a potentially ideal candidate for the treatment of postpartum anemia. To determine whether large-dose IV iron administration is an effective iron therapy, we conducted a randomized, controlled, noninferiority trial to compare the efficacy of IV ferric carboxymaltose with that of oral ferrous sulfate ($FeSO_4$) in the management of patients with early postpartum anemia.

MATERIALS AND METHODS

This was an open-label, phase 3, randomized, active control, noninferiority, multi-center trial conducted with institutional review board approval at each of 43 sites, including 40 in the United States and three in Mexico. In short, we screened patients for potential eligibility within 5 weeks before expected delivery date or early after delivery and, within 10 days after delivery, enrolled and randomly assigned eligible patients to receive either IV ferric carboxymaltose (Injectafer; American Regent, Inc, Shirley, NY) or oral iron therapy, then examined elements of efficacy and safety at intervals for the following 42 days.

We enrolled patients within 10 days after delivery who demonstrated a hemoglobin (Hb) of 10.0 g/dL or less, were using acceptable contraception or abstinence, and were able to give informed consent. The first patient was enrolled February 8, 2005, and the last patient completed, November 11, 2005.

We excluded patients who demonstrated previous nonadherence to prescribed oral iron therapy, history of anemia due to causes other than iron deficiency or blood loss secondary to pregnancy or delivery, estimated vaginal bleeding more than 100 mL in the 24 hours before randomization, active severe infection, serum transferrin saturation more than 50%, serum ferritin more than 500 ng/mL, serum creatinine more than 2.0 mg/dL, serum transaminases more than 1.5 times upper limit of normal, or evidence of untreated B12 or folate deficiency; had received erythropoiesis-stimulating agents (eg, recombinant erythropoietin) within 3 months before screening; or showed a history of myelosuppressive therapy, asthma under treatment, hepatitis, human immunodeficiency virus, or hematologic disorder other than iron deficiency.

Premature withdrawal was required if an intervention for management of anemia was given. We defined an anemia intervention as either a red blood cell transfusion, initiation of erythropoiesis-stimulating agents or iron administration not included in the study protocol. Intervention decisions, including the decision to transfuse, were made by physician discretion. Patients who wished to withdraw from the study could do so at any time without the need to justify the decision, and investigators could withdraw a patient at any time if withdrawal was felt to be in the best interest of the patient. In the analysis of efficacy and safety, we included data in each patient up to the time of withdrawal.

For patients assigned to IV ferric carboxymaltose, we calculated the total iron dose needed to correct anemia and replenish iron stores using the Ganzoni formula,[8] modified to include adjustment for baseline iron status:

Prepregnancy weight in kilograms$\times$(15–baseline Hb)$\times$ 2.4+500.

Fifteen is the target Hb in g/dL, 2.4 is a unitless conversion constant and 500 is the target iron stores in mg. Baseline Hb reflects the average of two Hb determinations (g/dL) obtained 12 hours or more apart and 18 hours or more postpartum, determined by local or point-of-care laboratory testing. If transferrin saturation was more than 20% *and* ferritin more than 50 ng/mL, 500 mg was subtracted.

Within 32 hours after determining baseline Hb, we initiated administration of the total calculated dose. The maximal dose administered in a single day was 15 mg/kg, not to exceed 1,000 mg. If the total calculated dose exceeded 1,000 mg, subsequent doses were administered weekly until the total dose was received, up to a maximal total dose of 2,500 mg. Intravenous iron was supplied as ferric carboxymaltose complex (American Regent, Inc., Shirley, NY), 500 mg elemental iron in 10 mL water. We adjusted injection volume and rate of administration by dose range as follows: 200 mg or less undiluted over 1–2 minutes; 300–400 mg in 100 mL normal saline over 6 minutes; 500–1,000 mg in 250 mL normal saline over 15 minutes.

For patients assigned to oral ferrous sulfate, we dispensed ferrous sulfate as 325-mg tablets (65 mg elemental iron) with instructions to take one tablet by mouth three times daily with 8 ounces of tap water, 1 hour before meals from day 0 until day 42. We dispensed tablets in blister packs of 25 tablets each, including one blister pack on days 0 and 7, and 2 blister packs on days 14 and 28. Used blister packs were returned to assess adherence to prescribed therapy.

Our hypothesis was that IV iron administration using ferric carboxymaltose complex is at least as effective as administration of oral iron in the correction of postpartum anemia. We chose ferrous sulfate as the comparator because administration of a ferrous salt is the accepted standard of care for treatment of postpartum anemia.

To examine efficacy, we defined the primary efficacy endpoint as the proportion of patients with a Hb increase 2 g/dL or more after treatment. Secondary measures of efficacy included the proportion of patients attaining a hemoglobin more than 12.0 g/dL (correction of anemia); the proportion achieving an increase in hemoglobin 3 g/dL or more; time to achieve the primary outcome; peak Hb increase from baseline; time to peak Hb increase; maximal increase in ferritin, transferrin saturation, reticulocyte count, or reticulocyte hemoglobin content; number of patients requiring intervention; time to intervention; proportion of patients with a Hb increase 2 g/dL or more and ferritin increase 160 ng/mL or more; and proportion of patients with improved quality of life. We used a central laboratory for all analyses of outcomes and local laboratories and point-of-care testing to determine Hb values needed to qualify for randomization or to calculate total iron dose.

We assessed health-related quality of life using normalized data from the Medical Outcomes Study Short Form 36 (SF-36) instrument, version 2[9] and the Fatigue Linear Analog Scale Assessment.[10] To normalize results, we first transformed item scores so that large values represented positive outcomes; transformed item scores were then summed to obtain dimension scores; and, finally, dimension scores were transformed to a 0–100 scale (worst-best) to obtain component scores. We defined a change from baseline that exceeded 0.5 standard deviation of the baseline mean as a minimally important difference.[11] The reference population for reporting normative SF-36 results for Physical Component Summary and Mental Component Summary scales were those obtained from a population survey of randomly selected, community-dwelling, 25- to 34-year-old U.S. females.[9]

To assess safety, we monitored blood pressure and recorded adverse events in all patients before, during, and after administration of IV iron and asked all patients to report any untoward medical event at its onset. We recorded adverse events from the day of consent through the completion of the study (day 42) or 30 days after the last dose of study drug, whichever was later. Investigators provided the onset and resolution date, severity, relationship to study drug, action taken, and outcome of the adverse event. We did not consider worsening anemia or iron deficiency to be adverse events, because these developments became study endpoints if an anemia intervention was required, as defined above.

To estimate sample size, we assumed that 80% of patients in each treatment group would be compliant with dosing and achieve the primary endpoint. Based on this assumption, a sample size of 160 patients per treatment group provided 85% power to achieve a 97.5% two-tailed confidence bound –15% or more for the treatment difference (IV iron minus oral iron) in success rate. The study was not powered for safety considerations.

Patients who had met all of the inclusion and exclusion criteria were stratified by Hb levels (9.1–10.0 g/dL, 8.1–9.0 g/dL, 8.0 g/dL or less) and requirement for cesarean delivery and screening iron indices (transferrin saturation more than 20% and ferritin more than 50 ng/mL, transferrin saturation 20% or less or ferritin 50 ng/mL or less). Stratified random treatment assignments were prepared using computerized random number generation, blocked randomization, and an interactive voice response system.

In the analysis of the primary efficacy endpoint, noninferiority was demonstrated if the one-tailed 97.5% confidence bound for the treatment difference in success rate (IV iron results minus oral iron results) was 15% or more. If the bound exceeded zero, superiority of IV iron to oral iron was demonstrated. The confidence bound was based on the normal approximation to the binomial distribution without stratification.

We determined the effect of baseline characteristics on the primary efficacy endpoint by logistic regression. Baseline covariates included Hb, ferritin, transferrin saturation, age, race, method of delivery (vaginal, cesarean delivery), estimated blood loss from delivery, and number of neonates delivered.

In the analysis of secondary efficacy endpoints, treatment differences in proportions were assessed with Fisher exact test. We estimated time-to-event

curves using the Kaplan-Meier method and examined for treatment group differences using the log rank test. We used repeated measures analysis to compare changes from baseline between groups.

RESULTS

Three hundred sixty-one (361) patients were randomly allocated at 43 centers to receive IV iron (as ferric carboxymaltose; 182 patients) or oral iron (ferrous sulfate; 179 patients). Of these 361 patients, eight assigned to IV ferric carboxymaltose and one assigned to oral iron discontinued from the study before dosing and were excluded from the evaluated population. The safety population included 352 patients who received at least one dose of treatment medication: 174 patients in the IV ferric carboxymaltose group and 178 in the oral iron group (Fig. 1). The intent-to-treat population, which formed the basis for efficacy analysis, included all safety patients except those who lacked at least one Hb determination after baseline (five IV ferric carboxymaltose patients; seven oral iron patients) and those who on review lacked Hb less than 11 g/dL at baseline (one IV ferric carboxymaltose patient, two oral iron patients). Accordingly, the intent-to-treat population consisted of 168 IV ferric carboxymaltose patients and 169 oral iron patients.

Of the safety population, 165 (94.8%) of the 174 patients in the IV ferric carboxymaltose group and 162 (91.0%) of the 178 patients in the oral iron group completed the study. The nine patients in the IV ferric carboxymaltose group who did not complete the study included four due to patient request, two due to adverse events, two lost to follow-up, and one received intervention (nonstudy iron).

The 16 patients in the oral iron group who did not complete the study included seven lost to follow-up, four discontinued due to adverse events, three found after randomization not to have met the selection or study compliance criteria and two discontinued due to patient request.

Among patients in the intent-to-treat population, there were no significant differences at baseline between patients in the IV ferric carboxymaltose group and those in the oral iron group in demographic descriptors, iron status, or severity of anemia (Table 1). Adherence to prescribed therapy was greater among patients in the IV ferric carboxymaltose group compared with those in the oral iron group (mean percent adherence 98.0% compared with 83.9%; 95% CI: 95.8–100.2 compared with 80.1–87.7). Five patients assigned to IV ferric carboxymaltose and 19 assigned to oral iron received less than 67% of the prescribed dose.

In the IV ferric carboxymaltose group compared with the oral iron group, there was no between-group

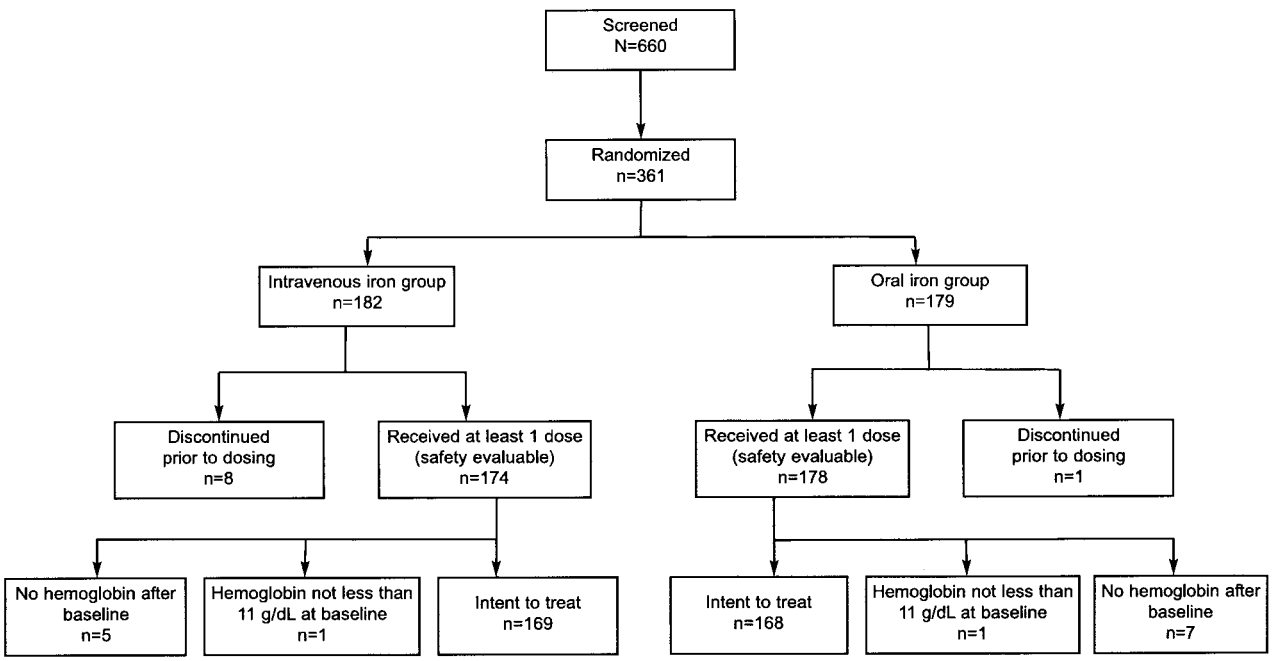

Fig. 1. Disposition of study participants by treatment assignment.
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difference in the proportion of patients who achieved the primary endpoint, a rise in Hb 2.0 g/dL or more within 42 days after baseline (96.4% compared with 94.1%, 95% CI –2.19 to 6.88, *P*=.443, Fig. 2). The CI for the differences in success rates demonstrated the noninferiority of ferric carboxymaltose relative to oral iron. However, the median time to achieve the primary endpoint (Hb rise 2.0 g/dL or more) was shorter in patients assigned to IV ferric carboxymaltose compared with oral iron treatment (7.0 compared with 14.0 days, *P*<.001). The proportion of patients who achieved a rise in Hb 3.0 g/dL or more was greater at each treatment interval after day 7 (Fig. 2), and the proportion of patients who experienced correction of anemia (achieving Hb mor than 12.0 g/dL) was higher both overall (90.5% compared with 68.6%, *P*<.001) and at each treatment interval in the IV ferric carboxymaltose group. Among patients assigned to oral iron, but not among those assigned to IV ferric carboxymaltose, the percentage of patients achieving Hb 12 g/dL or more decreased as the baseline Hb decreased. Between-group differences in efficacy were therefore greatest in those patients with the most severe anemia (Fig. 3). Moreover, among patients assigned to IV ferric carboxymaltose compared with those assigned to oral iron, the overall erythropoietic response (Hb, hematocrit [Hct], reticulocytes, mean corpuscular volume, mean corpuscular hemoglobin and reticulocyte hemoglobin content) was more robust at most treatment intervals (Fig. 4).

Serum ferritin increased promptly in the IV ferric carboxymaltose treatment group but failed to increase in the oral iron group. Differences between groups were significant at each study interval (Fig. 5). transferrin saturation increased significantly at every interval in both groups, related to a rise in serum iron and fall in total iron-binding capacity (TIBC); however, IV iron–treated patients showed higher transferrin saturation at each interval after the first week, associated with a more pronounced rise in serum iron and fall in TIBC (Fig. 5).

The completion rates for the health-related quality-of-life assessments in the IV ferric carboxymaltose and oral iron groups were 94.8% and 91.0%, respectively. In both treatment groups, baseline scores were lower than the expected normal values for the SF-36 physical component summary but above normal values for the mental component summary (Fig. 6). Patients assigned to IV ferric carboxymaltose or oral iron experienced similar increases in SF-36 scores and decreases in Fatigue Linear Analog Scale Assessment scores. Between-group differences were not significant at any study interval. The within-group change from baseline to day 42 met or exceeded criteria for minimum important difference for every health-related quality-of-life scale except SF-36 Role-Emotional.

The mean cumulative per patient dose of IV ferric carboxymaltose administered was 1,403.1 mg (95% CI of the mean 1,344.6–1,461.6) and the mean cumulative dose of oral iron was 6,764.0 mg (6,383.0–7,145.0). There were 350 total injections of IV ferric carboxymaltose administered: 17 patients (9.8%) received only one injection, 138 (79.3%) received two injections, and 19 (10.9%) received three injections. Of the 174 patients assigned to receive IV ferric

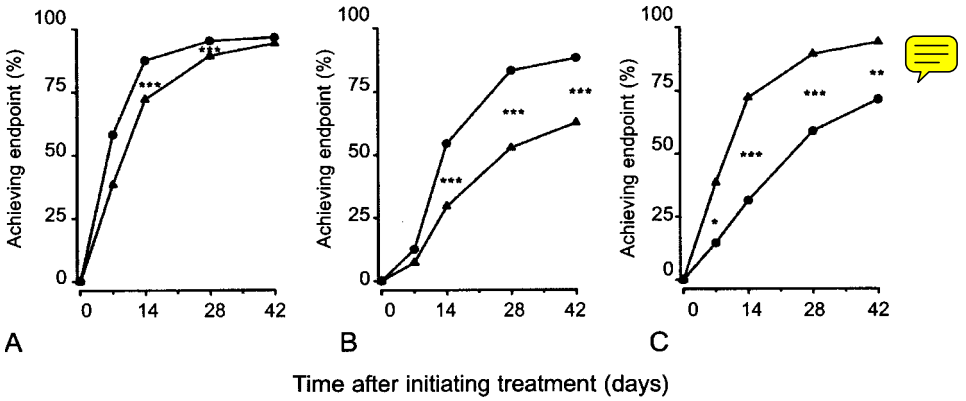

Fig. 2. Percentage of study participants achieving anemia endpoints according to treatment assignment (IV ferric carboxymaltose given on days 0, 7, or 14 or oral ferrous sulfate thrice daily on days 0–42). **A.** Primary study endpoint, Hb increase 2 g/dL or more. **B.** Secondary endpoint, Hb increase 3.0 g/dL or more. **C.** Secondary endpoint, achieved Hb 12.0 g/dL or more. Between-group comparisons: **P*<.05; ***P*<.01; ****P*<.001. *Solid line with circle,* intravenous ferric carboxymaltose; *solid line with triangle,* oral ferrous sulfate.

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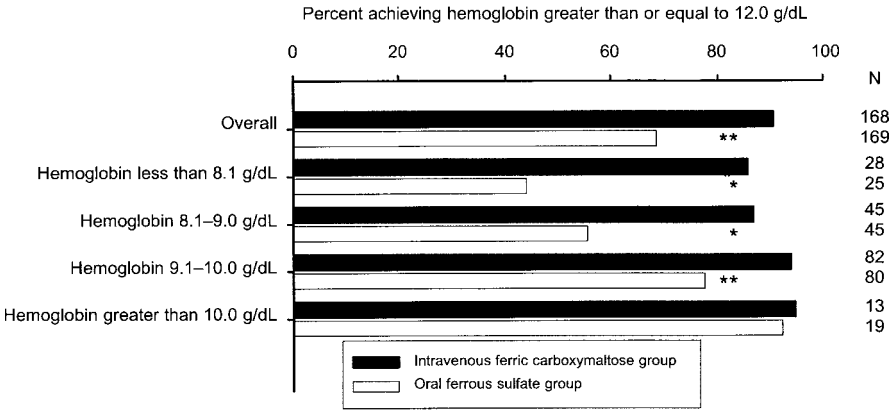

Fig. 3. Relationship between severity of anemia at baseline and probability of achieving a Hb 12.0 g/dL or more after iron therapy. Intravenous ferric carboxymaltose was given on days 0, 7, or 14 or oral ferrous sulfate thrice daily on days 0–42. Between-group comparisons: *$P<.05$; **$P<.01$.

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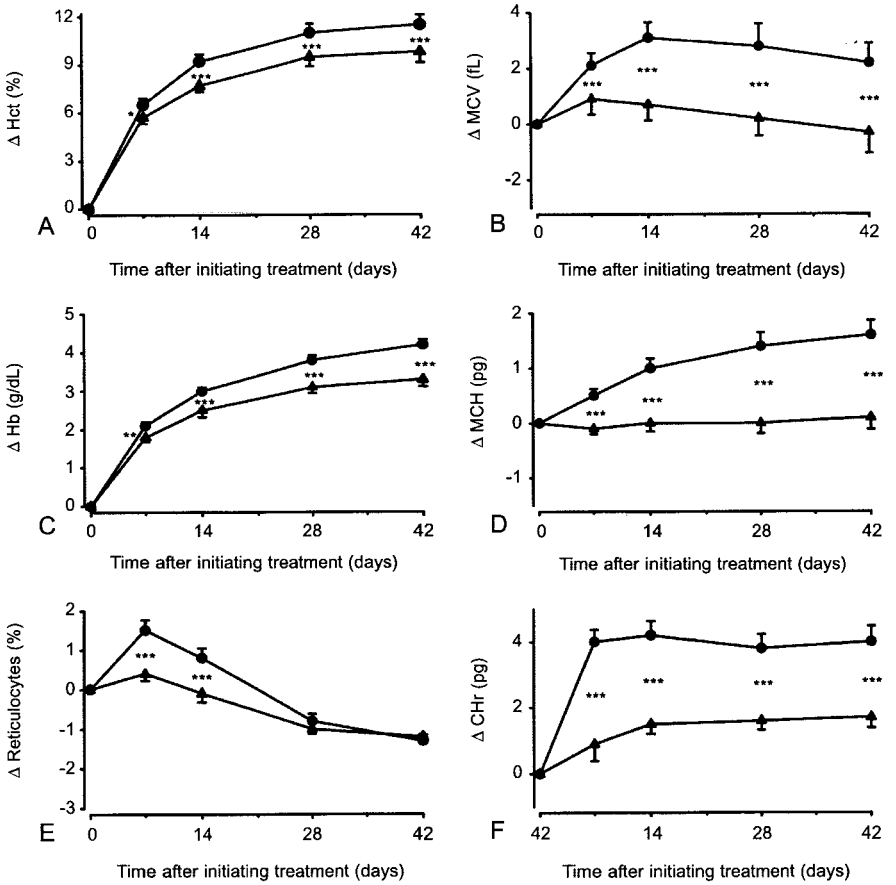

Fig. 4. Change in markers of hematologic response from baseline according to treatment assignment. **A.** Hematocrit (HCT). **B.** Mean corpuscular volume (MCV). **C.** Hemoglobin (Hb). **D.** Mean corpuscular hemoglobin (MCH). **E.** Reticulocytes. **F.** Content of hemoglobin in reticulocytes. Intravenous ferric carboxymaltose was given on days 0, 7, or 14 or oral ferrous sulfate thrice daily on days 0–42. *Solid line with circle,* intravenous ferric carboxymaltose; *solid line with triangle,* oral ferrous sulfate. Between-group comparisons: *$P<.05$; **$P<.01$; ***$P<.001$.

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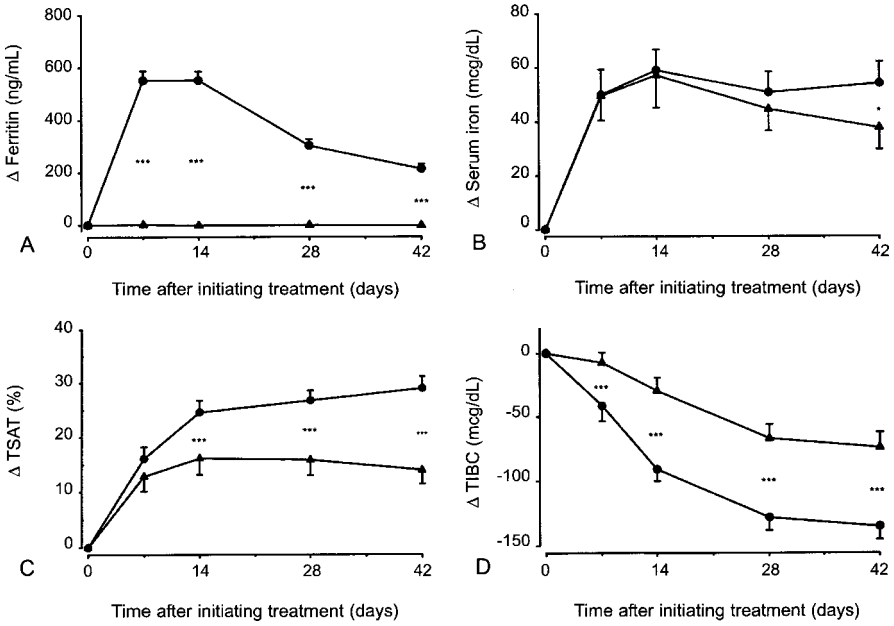

Fig. 5. Change in serum markers of iron status from baseline according to treatment assignment. **A.** Ferritin. **B.** Iron. **C.** Transferrin saturation (TSAT). **D.** Total iron binding capacity (TIBC). Intravenous ferric carboxymaltose was given on days 0, 7, or 14 or oral ferrous sulfate thrice daily on days 0–42. *Solid line with circle,* intravenous ferric carboxymaltose; *solid line with triangle,* oral ferrous sulfate. Between-group comparisons: *$P<.05$; ***$P<.001$.

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carboxymaltose, 151 (86.8%) received total doses that exceeded 1,000 mg.

No serious drug-related adverse events occurred in either treatment group. Patients assigned to oral iron therapy were more likely to report gastrointestinal complaints, particularly constipation and nausea, whereas those assigned to IV ferric carboxymaltose were more likely to experience skin disorders, principally mild pruritus and rash that usually occurred during or shortly after IV ferric carboxymaltose infusion and resolved within 5–15 minutes (Table 2). Eight patients received a second injection of IV ferric carboxymaltose after experiencing an episode of pruritus, rash, or both with the first injection; of these, three experienced recurrent findings, again mild and transient.

One patient assigned to oral iron developed depression and was discontinued from the trial. One patient assigned to IV ferric carboxymaltose (baseline Hb 7.9 g/dL) died 13 days after vaginal delivery, 7 days after IV iron injection, and autopsy confirmed peripartum cardiomyopathy. Neither event was considered by the investigator to be drug-related. There were 46 infections reported, 24 in the IV ferric carboxymaltose treatment group, and 22 in the oral iron treatment group (13.8% compared with 12.4%, $P=.753$). None were thought to be related to study drug. No episodes of phlebitis were reported in the IV ferric carboxymaltose treatment group.

Discontinuation of study drug due to drug-related adverse effects occurred in one patient assigned to the IV ferric carboxymaltose treatment arm and in five patients assigned to the oral iron arm. The patient assigned to IV ferric carboxymaltose experienced a pruritic rash described as probably related to study drug 3 days after receiving a 600 mg dose. Of the five patients in the oral iron treatment group, four discontinued due to gastrointestinal complaints (nausea, vomiting, or diarrhea) and one due to elevated serum transaminase.

We observed several statistically significant changes in nonhematologic clinical chemistry results during the course of the trial. Most changes showed no between-group differences, suggesting that they were related to the natural history of the postpartum condition (Tables 1–3). We saw a transient fall, however, in serum phosphate among patients in the IV ferric carboxymaltose treatment group which reached nadir at study day 14 (delta phosphate from baseline, -1.1 ± 0.77 compared with 0.0 ± 0.73 mg/dL, IV ferric carboxymaltose compared with oral iron, respectively, $P<.001$) and returned to baseline by day 42. Although mean serum phosphate was unchanged in

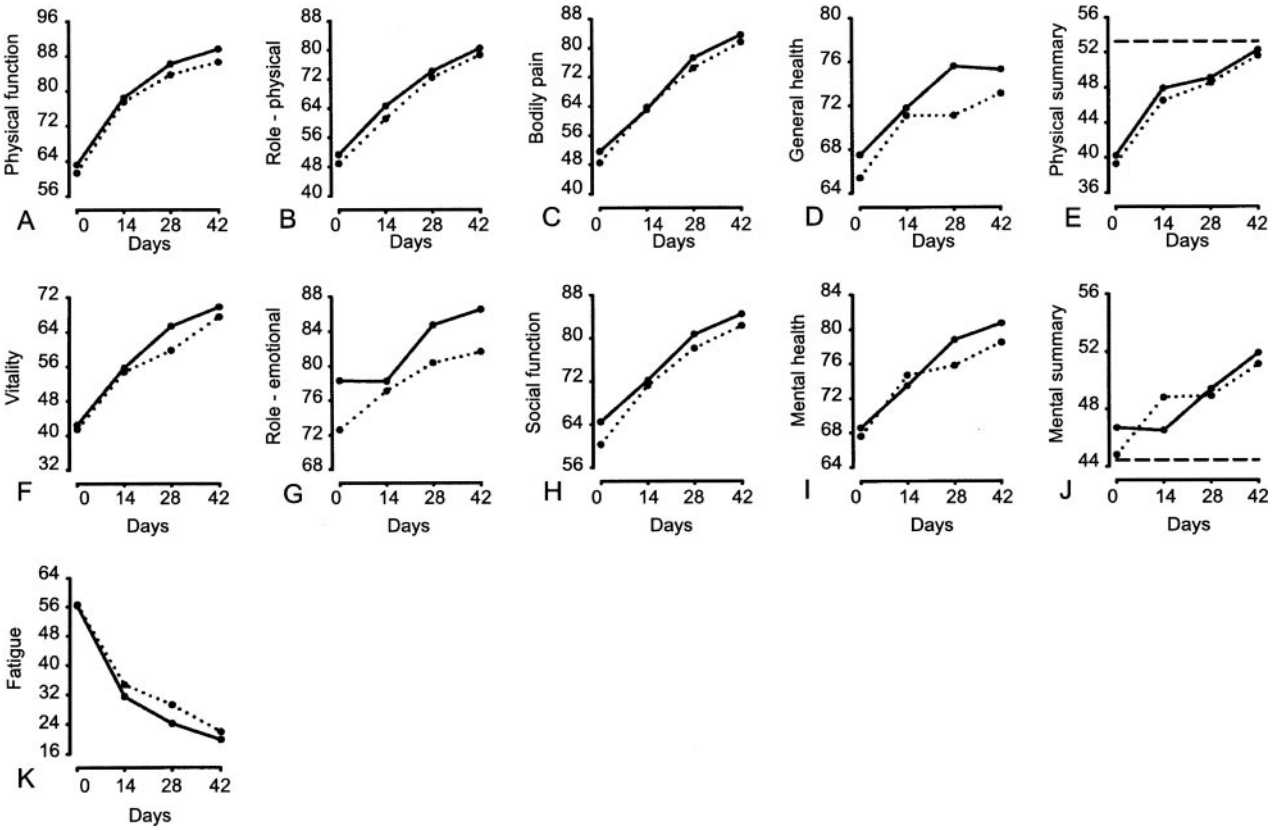

Fig. 6. Health-related quality of life in patients after iron treatment. Results are shown as mean scores of the Medical Outcomes Study Short Form 36 Health Survey (SF-36), including eight components (**A–D** and **F–I**) and two summary component scores (**E, J**) and as mean scores of the 10-cm Fatigue Linear Analogue Scale (**K**). Increases in SF-36 scores and decreases in Linear Analog Scale Assessment scores reflect improvement. Reference values for SF-36 summary component scores (**E, J**) are given for the general U.S. population of 25–34-year-old females.[9] *Solid line with circle,* IV ferric carboxymaltose; *dotted line with circle,* oral ferrous sulfate; *dashed line,* reference.

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the oral iron treatment group, in both treatment groups there was a highly significant relationship between baseline serum phosphate level and the maximal decrease in serum phosphate from baseline (IV ferric carboxymaltose Pearson's $r=-0.22$, $P=.004$; oral iron Pearson's $r=-0.69$, $P<.001$). The serum phosphate decreases after oral and IV ferric carboxymaltose therapy were highest in those with highest baseline serum phosphate. Serum calcium rose in both groups throughout the study, but the increase was slightly less in the IV ferric carboxymaltose group compared with the oral iron group at day 7 and 14 (delta calcium from baseline, 0.4 ± 0.5 compared with 0.6 ± 0.5 mg/dL, day 14, $P<.001$). Serum albumin increased in both groups (peak increase, mean±standard deviation: 1.4 ± 0.4 compared with 1.3 ± 0.4 g/dL, IV iron compared with oral iron, $P=.189$).

DISCUSSION

We undertook the current study to compare two treatments, IV ferric carboxymaltose and oral ferrous sulfate, for management of a common disorder, postpartum anemia. Our results provide new information not previously available on the efficacy of IV iron compared with oral iron therapy in managing postpartum anemia, the effect and reversibility of anemia on quality of life in postpartum patients, the rate of patient adherence to IV compared with oral iron treatment, the potential adverse effects and nonhematologic clinical chemistry changes after therapeutic iron intervention, and the use of ferric carboxymaltose complex for rapid IV administration of large iron doses.

The prevalence and potential adverse effect of postpartum anemia on women and infants, coupled with substantial drawbacks to use of currently avail-

Table 1. Baseline Demographics in the Intent-to-Treat Population

Baseline Characteristic	IV Ferric Carboxymaltose (n=168)	Oral Ferrous Sulfate (n=169)	*P*
Age (y)	26.9 (±6.4)	26.1 (±6.0)	.180
Weight (kg)	76.4 (±19.1)	81.0 (±19.7)	.035
Race			.231
White	88 (±52.4)	77 (±45.6)	
Hispanic	44 (±26.2)	51 (±30.2)	
African American	31 (±18.5)	37 (±21.9)	
Other	5 (±3.0)	4 (±2.4)	
Hb (g/dL)	9.0 (±0.9)	9.0 (±1.0)	.864
Hb category (g/dL, %)*			.857
9.1–10.0	81 (48.2)	86 (50.9)	
8.1–9.1	55 (32.7)	54 (32.0)	
8.0 or less	32 (19.0)	29 (17.2)	
TSAT (%)	10.6 (±9.0)	9.8 (±4.3)	.311
Ferritin (ng/mL)	26.1 (±36.6)	23.7 (±24.0)	.489
Previous treatment with oral iron	139 (±82.8)	145 (±86)	.458
Intolerance to previous oral iron agent (%)	6 (3.6)	4 (2.4)	.542

IV, intravenous; Hb, hemoglobin; TSAT, transferrin saturation.
Data in parentheses are standard deviation unless otherwise noted.
* At randomization.

able iron agents, render an IV iron agent that can be safely administered in one to three large doses a useful therapeutic asset. Clearly, both oral iron agents and currently available IV iron agents pose difficult challenges to effective management in this patient population. Oral iron agents are inexpensive and modestly effective. Anemic postpartum patients receiving oral iron, compared with their counterparts receiving placebo[12] or no treatment,[13] experience a more rapid increase in Hb, a more rapid correction of anemia, and a slight improvement in iron stores. However, GI complaints afflict up to 20% of patients taking ferrous iron salts,[14,15] as many as 30% of unselected patients may be totally nonadherent to prescribed therapy,[16] and efficacy hinges, of course, on prolonged, successful adherence to a twice or thrice-daily pill-taking regimen.[17]

True to previous experience, we found significant drawbacks to oral iron therapy. Although Hb and Hct increased in patients assigned to oral iron, some of this increase can be ascribed to the expected decrease in plasma volume that follows delivery.[13,18] We found that patients in the oral iron treatment group showed little discernable evidence of improved adequacy of iron supply for erythropoiesis as measured by transferrin saturation, reticulocyte hemoglobin content, mean corpuscular volume, mean corpuscular hemoglobin, or reticulocyte count or improved iron stores as measured by serum ferritin. Previous trials have shown that postpartum patients treated with oral iron, when compared with those receiving placebo only, correct anemia earlier,[13] achieve higher levels of Hb, ferritin, transferrin saturation, and stainable bone marrow iron and achieve lower levels of TIBC, soluble transferrin receptor (sTfR), and percent hypochromic red cells.[12,18] Although peak Hb response

Table 2. Adverse Reactions by More Than 2% of Patients (Safety Population) in Either Treatment Group, by Classification, Considered to Be Drug-Related by Investigator

Adverse Event Classification	IV Ferric Carboxymaltose (n=174)	Oral Ferrous Sulfate (n=178)	*P*
All GI disorders	11 (6.3)	43 (24.2)	<.001
Constipation	6 (3.4)	20 (11.2)	.007
Diarrhea	0 (0.0)	7 (3.9)	.015
Nausea	2 (1.1)	13 (7.3)	.006
Pruritus, rash, or both	9 (5.2)	4 (2.2)	.164
Serum transaminase elevation	1 (0.6)	5 (2.8)	.215
Headache	10 (5.7)	5 (2.8)	.196

IV, intravenous; GI, gastrointestinal.
Data are n (%).

with or without treatment is seen within 4 weeks postpartum, any continued improvement in iron status thereafter requires continued oral iron administration.[12] Taken together with these reports, our findings are in keeping with the conclusion that postpartum patients receiving oral iron therapy for 6 weeks show little evidence of improved iron stores, limited improvement in adequacy of iron supply for erythropoiesis, and a modest boost to Hb and Hct.

The conclusion that oral iron efficacy is limited may be explained in part by frequent GI complaints and high rates of nonadherence with prescribed therapy. Nonadherence to oral iron prescription is directly related to severity of GI symptoms,[14] and efficacy is known to diminish as nonadherence increases.[14,16] We found that both GI complaints and nonadherence were higher among patients assigned to oral iron therapy than in those assigned to IV ferric carboxymaltose. Clinicians are likely to encounter higher rates of nonadherence than we observed, because study patients were selected for willingness to participate and absence of previous intolerance, were given iron tablets rather than prescriptions, and received regular encouragement from study personnel.

By comparison, large-dose administration of ferric carboxymaltose showed robust evidence of efficacy, tolerability, and safety. We confirmed that IV ferric carboxymaltose is at least as effective as oral iron in achieving the primary endpoint, a Hb increase 2.0 g/dL or more. Importantly, more than 90% of patients received the calculated iron replacement in only one or two ferric carboxymaltose doses, no serious adverse reactions were observed, and only one patient discontinued treatment due to drug-related effects (rash and pruritus).

In multi-center clinical trials to date, a total of 4,903 doses of ferric carboxymaltose have been given to 2,065 patients without serious drug related adverse drug events (data on file, Luitpold Pharmaceuticals, Norristown, PA). The mean maximal single dose in these trials was 800 mg (±295 standard deviation). By contrast, to avoid hypotension and other dose-related adverse drug effects, administration of currently available IV iron agents is limited to 100 mg of iron dextran over 2 minutes, 125 mg of ferric gluconate over 10 minutes, or 200 mg of iron sucrose over 2–5 minutes. Higher doses of iron sucrose are U.S. Food and Drug Administration–approved, but only for slow IV administration (up to 400 mg over 2.5 hours) and only for specific indications in chronic kidney disease. In short, ferric carboxymaltose complex seems to afford the efficacy of IV iron administration without the inconvenience of multiple small-dose injections, the long infusion times and risk of adverse drug effects associated with higher IV iron doses, and the inconvenience, adverse GI effects, and risk of nonadherence associated with thrice-daily oral iron therapy.

Table 3. Baseline Clinical Laboratory Values and Change From Baseline in Postpartum Patients Assigned to Intravenous Iron or Oral Iron Treatment (Safety Population)

	IV Ferric Carboxymaltose			Oral Ferrous Sulfate			
Analyte	Baseline	Change at Day 42	Within-Group Significance of Change *P*	Baseline	Change at Day 42	Within-Group Significance of Change *P*	Between-Group Comparison of Changes *P*
Albumin (g/dL)	2.9	1.3	<.001	2.8	1.3	<.001	.331
C-reactive protein (mg/dL)	4.5	–4.0	<.001	4.9	–4.4	<.001	.471
ALT (units/L)	24.7	4.8	.041	23.4	3.7	.066	.726
AST (units/L)	27.0	–3.4	.041	25.4	–1.2	.361	.321
Alkaline phosphatase (units/L)	129.0	–25.9	<.001	128.4	–31.0	<.001	.178
GGT (units/L)	14.7	5.3	.079	16.0	–0.4	.805	.096
LDH (units/L)	279.6	–102.8	<.001	281.4	–98.7	<.001	.656
Creatinine (mg/dL)	0.6	0.1	<.001	0.7	0.1	<.001	.949
Urea nitrogen (mg/dL)	11.1	1.5	<.001	10.3	1.8	<.001	.419

IV, intravenous; ALT; alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyltransferase; LDH, L-lactate dehydrogenase.

Health-related quality of life and transfusion requirements constitute the direct patient outcomes most likely to be affected by anemia and reversible with iron therapy. In a randomized control trial in patients with moderate postpartum anemia (Hb more than 10.0 g/dL), quality-of-life improvement, in parallel with anemia correction, occurred earlier among patients treated with oral iron than among untreated patients.[13] In the current trial, we confirmed that untreated women with postpartum anemia suffer substantial health-related quality-of-life morbidity, evidencing particularly poor scores for fatigue, physical function and vitality. Our results also show that early intervention with effective iron therapy, regardless of the route of administration, dramatically improves health-related quality of life in women with postpartum anemia. Generalization of the health-related quality-of-life results from the current trial to clinical practice is, however, limited by the low numbers of study patients with severe anemia (less than 20% of patients in either treatment group with Hb less than 8.0 g/dL), use of measures to maximize oral iron adherence that are not commonly available in practice (provision of tablets, early and frequent follow-up, pill-counting, counseling for nonadherence), and the lack of information on maternal–infant behavior and infant development. Finally, no patient in either treatment arm received red blood cell transfusion, consistent with previous findings that transfusion therapy after vaginal or caesarian delivery is uncommon.[19]

We serially examined a number of routine clinical laboratory chemistries in addition to markers of hematologic and iron status response. For most analytes, including serum albumin, C-reactive protein, hepatic enzymes, creatinine, and urea nitrogen (Table 3), the changes we observed followed the expected postpartum course.[20] However, we also saw a consistent, asymptomatic, and transient decrease in serum phosphate among patients assigned to IV iron therapy. Significant hypophosphatemia has been reported early after initiation of hemolytic anemia,[21] during recovery from aplastic crisis associated with hereditary spherocytosis,[22] and during reconstitution of hematopoiesis after allogeneic peripheral blood stem cell transplantation,[23] suggesting that cellular uptake of phosphate during accelerated erythropoiesis may be sufficient to acutely lower extracellular phosphate concentration. Alternatively, a fall in serum phosphate may reflect correction of intracellular phosphate depletion, a condition described after induction of iron deficiency in experimental animals.[24,25] We found that the degree of phosphate decrease was related to baseline phosphate level: the higher the baseline serum phosphate, the greater the observed maximal decrease after iron therapy. Because we observed a similar relationship in both the IV and oral treatment arms, the greater degree of phosphate fall in the IV iron–treated patients likely reflects greater efficacy of IV iron in either stimulating erythropoiesis, replenishing iron stores, or both and that the mechanism of phosphate lowering is intrinsic to iron therapy.

To apply findings of the current study to treatment of unselected patients with postpartum anemia, several specific limitations of our study and those of others should be considered. First, our results showing superior efficacy of IV iron over oral iron are not consistent with the negative findings of the single previous RCT comparing oral iron, IV iron, and IV iron plus epoetin alfa.[6] However, treatment groups in that trial were small (n=20 each), the observation period was short (14 days), and the total dose of iron sucrose was limited to 800 mg (200 mg IV per day on days 1–4). By contrast, our study included results from more than 160 patients in each treatment arm followed for 42 days and given iron doses calculated to both correct anemia and replenish iron stores. Second, our information on the efficacy of oral iron is limited to 42 days of administration. Continued administration of oral iron therapy up to 12 weeks postpartum has, however, been previously examined in a small trial.[12] Beyond 4 weeks, continued oral iron therapy is associated with no further increase in Hb or ferritin, a slight increase in transferrin saturation, and a progressive decline in percent hypochromic red cells and sTfR.[12] Thus, prolongation of oral iron therapy beyond 28 days may increase adequacy of iron for erythropoiesis (as indicated by changes in transferrin saturation, percent hypochromic red cells and sTfR) but does not seem to afford a further increase in Hb or iron stores (as reflected by serum ferritin). Finally, longer trials will be needed to confirm whether the higher iron stores achieved in IV iron–treated patients signify a persistent treatment benefit in women with ongoing menses or subsequent pregnancy.

These limitations notwithstanding, our results are important for clinicians because they shed new light on the severity of quality-of-life deficits associated with postpartum anemia, confirm that effective iron therapy corrects both the anemia and the quality-of-life deficits, and describe evidence for a new therapeutic option, an iron agent that can reduce the need for multiple IV iron infusions.

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