Intravenous Iron Versus Oral Iron in the Treatment of Postpartum Iron Deficiency Anemia

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Abstract

Background: Postpartum anemia can develop after delivery because of unforeseen medical problems during and after delivery which could complicate a mother's ability to properly care for her newborn child. The current treatment for postpartum anemia is oral iron supplementation but this treatment has been associated with several gastrointestinal side effects. Alternative treatments include blood transfusions and intravenous (IV) iron therapy. Since blood transfusions are very costly, IV iron treatments have become more popular.

Objectives: The objective of this review is to evaluate the hematological parameters and quality of life of women with postpartum anemia while being treated with IV iron sucrose or IV ferrous carboxymaltose compared to oral ferrous sulfate.

Methods: An exhaustive search of available medical literature was performed using three databases: MEDLINE, EMBASE and CINAHL. All keywords were originally searched individually and then combined to refine the search. The inclusion criteria consisted of randomized control trials (RCT) published in English after January 2000, which looked at hematologic parameters in postpartum anemic women being treated with either an oral iron supplement or IV iron therapy.

Results: Six RCTs involving 1140 women were reviewed. Four of the studies showed that anemia was corrected with iron therapy at some point during the trial regardless of the treatment method. Three studies showed a significantly decreased amount of time to increase hemoglobin (Hb) levels in the women who where treated with IV iron therapy. All of the studies showed a significant increase in ferritin levels in the IV iron therapy group when compared to the oral iron group, with five of the six studies ending their studies with significantly continued ferritin elevation in the IV iron group. The two studies that examined maternal quality-of-life parameters reported non-significant improvements in the IV treatment group. Although both of these studies also assessed maternal fatigue, only one study reported significant declines in physical and total fatigue.

Conclusion: Both ferric carboxymaltose and iron sucrose are safe and effective ways to treat postpartum iron deficiency anemia. Both forms of IV iron are superior to oral ferrous sulfate as they require a shorter treatment period, increase the likelihood of compliance, have no gastrointestinal side effects and rapidly replenish iron stores.

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Intravenous Iron Versus Oral Iron in the Treatment of Postpartum Iron Deficiency Anemia

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Biography

[Redacted for privacy]
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**Keywords:** postpartum anemia, intravenous iron, oral iron, ferric carboxymaltose, ferrous sulphate, anemia, iron deficiency.
Acknowledgements

To my parents

To my siblings,

Dr Nation and Nurse Ann…

To my friends…

To Tad…
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List of Abbreviations

BID Twice a Day
Hb Hemoglobin
IDA Iron Deficiency Anemia
ITT Intent-to-treat
IV Intravenous
mITT Modified Intent-to-treat
RCT Randomized Controlled Trials
TID Three Times a Day
SF-36 Medical Outcomes Study Short Form 36
Intravenous Iron Versus Oral Iron in the Treatment of Postpartum Iron Deficiency Anemia

BACKGROUND

Overview

Childbirth should be a joyous event. However, unforeseen medical problems such as postpartum hemorrhage or postpartum anemia can develop and make this time very difficult. The physiological effects of pregnancy and blood loss at birth can exacerbate anemia. Blood loss from delivery is one of the most common causes of anemia. In the United States, about a quarter of the women who did not have anemia during pregnancy became anemic during the postpartum period. Depending on the severity of the blood loss, postpartum anemic women can be at a greater risk for morbidity and mortality. Of the 515,000 maternal deaths worldwide in 1995, 20% were attributed to anemia.

The World Health Organization (WHO) defines iron deficiency anemia (IDA) as a hemoglobin (Hb) of less than 12 g/dL. The current gold standard for checking for IDA includes looking at both the Hb levels and the serum ferritin values. Ferritin is a protein that stores iron and releases iron as needed; it is the body’s regulator against iron deficiency. By the time a patient is anemic they have already depleted their iron storage, as evidence by decreased levels of serum ferritin. However ferritin can be falsely elevated because of a secondary inflammatory response. Although ferritin alone cannot accurately predict IDA, it has been shown to have a possible association with depression and impairment of short-term memory.
According to the National Pregnancy Nutrition Surveillance System, 29.8% of women who were not previously anemic during pregnancy become anemic after delivery.\textsuperscript{8} Consequences of postpartum IDA have been associated with fatigue, depression, cognitive dysfunction, stress, and anxiety.\textsuperscript{9} It can also interrupt mother-child bonding. Studies have shown that infants of anemic mothers were developmentally delayed, possibly due to the fact that anemic mothers were significantly more “negative” towards their baby, engaged less in goal setting, and were less “responsive” than non-anemic mothers.\textsuperscript{10}

Fatigue alone can be difficult to manage. It can affect a person’s physical and mental health, their motivation to participate in everyday activities and even the desire to interact socially. The everyday challenges of fatigue are significantly compounded after childbirth. In addition to a new mother’s demanding tasks of caring for a child, postpartum fatigue can impact her postpartum maternal role attainment and may place her at greater risk for postpartum depression.\textsuperscript{11} Studies have shown that low Hb levels are significantly related to postpartum depression and postpartum fatigue.\textsuperscript{11}

Currently, the standard treatment for anemia is oral iron supplementation. However, this is limited by patient noncompliance and gastrointestinal symptoms such as nausea, vomiting, and diarrhea.\textsuperscript{12} Absorption of oral iron is influenced by the dosage, the patient’s iron storage, and the proximity of taking the medication relative to mealtime. Ideally, the supplement should be taken on an empty stomach as food can impair its absorption.\textsuperscript{13} This method of treatment is slow to take effect, often requiring several weeks for results to transpire.
Alternative treatment methods for anemia include intravenous (IV) iron therapy or blood transfusion. Blood transfusions are very costly and come with great risk, contributing to the increased popularity of IV iron therapy treatment.\(^5\) Hematologic changes, like Hb and ferritin, are fairly rapid with IV iron therapy and have a positive effect on the body’s iron storage which is measured by the ferritin level.

Intravenous iron administration with iron sucrose has been available for several years and is routinely used in a number of European countries to treat severe anemia.\(^{14}\) Iron sucrose has an excellent safety record, unlike older IV formulations such as ferrous dextran, which has been associated with a significant risk of anaphylactoid reactions.\(^{15}\) Intravenous iron sucrose can be administered as an infusion in small doses (about 200mg) over a 30-minute time period.\(^{16,15}\) A new IV iron preparation, ferric carboxymaltose, has been recently developed. It provides rapid replacement of iron storage and can be administered in higher single doses of up to 1000mg during a minimum administration time of less than 15 minutes.\(^{1,12,16}\) Despite its advantages, this treatment option is not readily available as it is currently not FDA approved.

**Purpose of the Review**

Iron deficiency anemia is common in postpartum women and has been linked to postpartum fatigue and poor health outcomes.\(^{17}\) Thus, it is important to determine if there is a more effective way of treating postpartum anemia. The primary objective of this systematic review is to determine whether using IV iron reduces the length of time required to resolve postpartum anemia. The secondary objective is to look how the resulting postpartum anemia impacts maternal quality of life and mother-child relations.
This review compares treatment outcomes between the use of using either IV ferric carboxymaltose or IV iron sucrose in comparison with oral ferrous sulfate for the treatment of postpartum anemia. The impact of the restoration of a mother’s iron storage on her quality of life will also be assessed.

METHODS

Search Strategy

An exhaustive search of the current literature was performed using the research databases MEDLINE, EMBASE and CINAHL. The keywords iron-deficiency anemia, postpartum anemia, ferric carboxymaltose, iron sucrose, and ferrous sulfate were used. Relevant studies were then reviewed and critiqued according to the inclusion and exclusion criteria discussed below.

Inclusions/Exclusions

The inclusion criteria for this review required all studies to be randomized controlled trials (RCT) published in English and after January of 2000. The studies must evaluate hematological parameters in postpartum anemic women and how they respond to the treatment of postpartum anemia by either an oral iron therapy or an intravenous (IV) iron therapy. All other studies were excluded if they did not meet these specific inclusion criteria.

RESULTS

After an extensive search of the literature, six randomized control trials (RCT) involving approximately 1140 women were included in this systematic review (See Table
Half of the studies compared treatment of intravenous (IV) ferric carboxymaltose to treatment with oral ferrous sulfate,\cite{1,12,16} while the other half compared treatment with IV iron sucrose to treatment with oral ferrous sulfate.\cite{14,18,19} All the studies used hematological parameters to report their results, including hemoglobin (Hb) and ferritin levels. Two of the studies reported results on health-related quality of life variables (e.g. fatigue, physical function, mental health, body pain, etc).\cite{16,19} Treatment regimens for each study are outlined in Table 2.

**Breymann et al**

Breymann et al\cite{18} conducted a RCT of 60 postpartum anemic women in Switzerland from a single center, with a Hb of <10g/dL at 24-72 hours post delivery, to compare the efficacy between recombinant human erythropoietin plus IV iron sucrose (will not be discussed because lack of relevance to this review), versus IV iron sucrose alone, versus oral iron supplementation alone. The hematologic parameters were measured on days 0, 4, 7, and 14. At baseline, the groups did not differ characteristically or hematologically. Three groups of 20 women were randomized using sealed envelops containing numbers allocated to one of three groups and started treatment within 48-72 hours after delivery. Baseline Hb and ferritin levels in the IV iron sucrose group and the oral iron supplementation group were 11.9g/dL and 12.2µg/L, respectively. The study reported that all patients completed the study with 100% compliance to study treatments protocols. The Hb levels increased steadily from baseline, but there was no statistical significance between the two groups. The ferritin levels, however, significantly increased in the IV iron sucrose group to 162.3µg/L (p<0.01) by day 4. The levels remained
elevated but fell slightly at the end of the trial, ending at 81.5µg/L (p< 0.01), compared to 29.7µg/L and 21.7µg/L in the oral group on days 4 and 14, respectively.¹⁸

Bhandal et al

Bhandal et al¹⁴ conducted a RCT of 44 postpartum anemic women in the United Kingdom with a Hb of <9g/dL and a ferritin of <15µg/L at 24-48 hours post delivery, to evaluate various hematological parameters at days 0, 5, 14 and 40. The study population was formed from a single center, where half of the women receiving IV iron sucrose (treatment group) and the other half receiving oral ferrous sulfate (control group). The study was able to evaluate results from 43 women all of whom strictly complied with the treatment regimens. The single exclusion occurred after randomization when one patient suffered a secondary postpartum hemorrhage that required a blood transfusion, excluding her from further participation in the study. The two groups were characteristically and hematologically similar at baseline, with Hb levels of 7.3g/dL and 7.5g/dL and ferritin levels of 13.0µg/L and 11.0µg/L in the IV treatment group versus the oral control group, respectively. The results indicated that both groups showed improvements in Hb levels throughout the study with higher levels in the IV group on days 5 and 14 (p<0.01). The IV group had a mean increase in Hb level from baseline at day 5 of 2.5g/dL compared to the oral group of 0.7g/dL. However, by day 40 there was no significant difference between the groups regarding the Hb level. Ferritin levels in the IV treatment group showed a significant response by day 5, with levels at 48.0µg/L (p<0.01), and remained elevated for the duration of the study, ending at 42.2µg/L (p<0.05). The group treated with oral iron supplementation had no increase in ferritin levels throughout the study.¹⁴
Westad et al

Westad et al\textsuperscript{19} conducted a RCT of 129 postpartum anemic women in Norway from five obstetric departments, each with a Hb of $\geq 6.5\text{g/dL}$ and $\leq 8.5\text{g/dL}$ within 48 hours after delivery, to compare the effect of IV iron sucrose to oral ferrous sulfate supplementation on hematological parameters and quality of life. The treatment group received IV iron sucrose and the control group received oral ferrous sulfate. The women were followed up at 4, 8, and 12 weeks with blood sampling and assessments of quality of life parameters. Both the Medical Outcomes Study Short Form 36 (SF-36) and the Fatigue Scale were utilized to assess quality of life parameter. Of the 129 women who entered the trial, one dropped out prior to receiving any treatment and 35 patients either withdrew from the study at their own request, experienced an adverse event with study medication, or were lost to follow-up. The study reported 95% compliance with the IV iron sucrose. The compliance with oral treatment was less than 50% among both groups; this percentage took into account both groups because the IV treatment group started taking oral ferrous sulfate at the end of week 4. The analysis of the results was based on an intent-to-treat (ITT) principle. After 4 weeks, the mean Hb levels of both groups increased, however there was no significant difference between the groups. The treatment group’s Hb level increased from 7.9g/dL to 11.9g/dL and the control group’s Hb level increased from 7.7g/dL to 12.3g/dL. Hemoglobin levels continued to increase from week 4 to week 8 with no significant difference between the groups, and then leveled off around week 8 for both groups. The non-significant hemoglobin results included patients who received blood transfusions. There was a significant increase in ferritin levels from the time of inclusion to week 4. The ferritin level in the treatment
group increased from 26.0µg/L at baseline to 40.0µg/L at week 4 (p<0.001). The oral control group showed very little change in ferritin levels throughout the study. At week 8 and 12, there were no significant differences between the groups with regard to the ferritin levels.\textsuperscript{19}

This study used the SF-36 to look at four main measures of a mother’s quality of life: the physical function score, the pain index, the vitality score, and the mental health score. All scores improved throughout the study. Although the changes were not significantly in favor of the treatment group throughout the study, at week 12 there was a significant difference in the pain index in favor of the treatment group. The Fatigue Score comprised physical, mental, and total fatigue ratings. In both groups the physical fatigue scores improved and the IV treatment group showed significantly greater improvements at weeks 4, 8 and 12 (p=0.02, p=0.02, p=0.03, respectively). The mental fatigue score did not change between the groups. Overall, the total fatigue score was significantly better in the treatment group after 4, 8, and 12 weeks (p=0.02 at each evaluation point).\textsuperscript{19}

A sub-analysis of 113 women was conducted to exclude patients who required blood transfusions. This sub-analysis showed a significantly higher proportion of subjects treated with IV iron sucrose achieved a HB of at least 2g/dL (p=0.04). Also, the treatment group showed significantly higher mean Hb levels at weeks 8 and 12 (p=0.02).\textsuperscript{19}

\textbf{Breymann et al}

Breymann et al\textsuperscript{12} randomized 349 postpartum anemic women from twenty centers in Romania, Russia, and Poland, with a Hb of \( \leq 10.5 \)g/dL, to compare the efficacy
between IV ferric carboxymaltose compared with oral ferrous sulfate. This was a multi-
center, open-label RCT. Patients were randomized according to a 2:1 ratio of ferric
carboxymaltose to ferrous sulfate with stratification by country and severity of anemia.
All patients received their first dose of medication within 7 days postpartum and then
attended follow-up visits after 1, 2, 4 and, 12 weeks. The groups did not differ at
baseline in characteristics or hematologically. Baseline Hb and ferritin levels in the IV
treatment group and in the oral iron supplementation group were 9.67g/dL and 39.9µg/L,
respectively. The results reported were based on efficacy results from the pre-protocol
analysis of 268 women which excluded women who had major protocol deviations or
who discontinued the study prematurely because of patient request, adverse events, non-
compliance or loss to follow-up during the study.12

The study also did an ITT analysis, which was not reported unless it differed from
the per-protocol analysis because the results were similar. There was a mean compliance
of greater than 90% in the oral group and, with the exception of two patients, 100%
compliance in the ferric carboxymaltose group. Hemoglobin levels in both groups
increased throughout the study but these increases were not significant at any time during
the study. Despite the non-significant results, the Hb levels of the IV treatment group did
rise more rapidly by week 1 when compared to the oral control group. Ferritin levels in
the treatment group, however, increased significantly throughout the study. At week 1
the ferritin levels of the treatment group were significantly elevated at 568.2µg/L, while
the control group showed only minimal increases at week two of 34.8µg/L. By the end
of the study there was still a significant elevation in the IV treatment group’s ferritin
level, compared to that of the oral control group (161.2µg/L versus 43.3µg/L, respectively).\textsuperscript{12}

\textbf{Van Wyck et al}

Van Wyck et al\textsuperscript{16} conducted an open-label, phase III, randomized, active control non-inferiority, multi-center trial from February 8, 2005 to November 11, 2005, including 361 postpartum anemic women from 43 sites (40 in the United States and 3 in Mexico) to determine the efficacy of rapid, large-dose IV ferric carboxymaltose to oral iron supplementation as evidenced by hematologic parameters and maternal health related quality of life assessments. Patients were enrolled in the study within 10 days postpartum, with Hb of 10.0g/dL or less. Subjects were excluded for any of the following reasons: previously demonstrated non-adherence to prescribed iron therapy, history of anemia due to causes other than iron deficiency anemia (IDA) or blood loss secondary to pregnancy or delivery, estimated vaginal bleeding more than 100mL in the 24 hours prior to randomization, active severe infection, serum transferrin saturation of more than 50\%, serum ferritin more than 500µg/L, serum creatinine more than 2.0mg/dL, serum transaminases more than 1.5 times upper limit of normal, evidence of untreated B12 or folate deficiency, received erythropoiesis-stimulating agents within 3 months before screening, history of myelosuppressive therapy, asthma under treatment, hepatitis, human immunodeficiency virus, or hematologic disorder other than iron deficiency. Nine women dropped out prior to initial dosing, therefore, 352 women were included in the safety population. Twenty-five women in the safety population did not complete the study because of patient request, adverse events (pruritic rash, nausea, vomiting or diarrhea, non-drug-related depression and a non-drug-related death), loss to follow-up,
not meeting study criteria, or taking iron supplements not approved by the study protocol. The results were based on the ITT population (168 women in the IV treatment group and 169 women in the oral control group) which consisted of all the safety patients except 15 women who either did not have at least one Hb lab reading drawn after baseline, or patients who did not have a Hb of less than 11g/dL at baseline. Among these patients, there was no significant difference at baseline between patients in either the treatment or the control group in demographics characteristics, iron status, or severity of anemia. The study reported a 98% compliance rate in the treatment group compared to 83.8% in the oral group.16

At the end of the study, there was no difference between the IV treatment group and the control group in the number of patients who achieved a rise in Hb 2.0g/dL or more within 42 days after baseline (96.4% versus 94.1%, p=0.443). Patients assigned to the IV treatment group achieved Hb rise of 2.0 or more in less time than the oral control group (7 versus 14 days, p<0.001). At each treatment interval after day 7, the proportion of patients who achieved a rise in Hb 3.0g/dL or more was greater in the IV treatment group. The IV treatment group also had a greater proportion of patients who experienced a correction of anemia (achieving Hb more than 12.0g/dL) at each treatment interval and overall (90.5% versus 68.6%, p<0.001) (Figure 1). The patients with the most severe anemia showed the greatest improvement in anemia correction when treated with IV ferric carboxymaltose. The IV ferric carboxymaltose promptly increased serum ferritin levels, while the oral group showed no increase. The groups showed significant differences at each study interval.16
The scores from the SF-36 at baseline for both groups were lower than expected for the physical component, and exceeded expectation for the mental portion but groups were similar at baseline. Both groups experienced similar increases in SF-36 and decreases in Fatigue Linear Analog Scale Assessment scores. However the difference between the groups was not significant at any point in the study.\textsuperscript{16}

\textbf{Seid et al}

Seid et al\textsuperscript{1} conducted a multi-center, RCT, including an ITT population of 291 postpartum anemic women in the United States from 28 centers from May 9, 2006 to December 27, 2006. The purpose was to evaluate the efficacy, safety, and tolerability of IV ferric carboxymaltose (treatment group) when compared to the oral ferrous sulfate (control group). Healthy postpartum anemic women who had delivered a child within 10 days of starting the study with a Hb 10g/dL or less were included. Excluded subjects had significant vaginal bleeding in the 24 hours prior to randomization, a history of anemia other than IDA or blood loss due to delivery, were undergoing treatment with myelosuppressive therapy or asthma therapy, had had recent blood transfusions, or erythropoietin within 3 months prior to screening. Subjects were stratified according to average baseline Hb levels (8.0 or less, 8.1-9.0, 9.1-10.0g/dL), requirements for cesarean, and screening ferritin levels (25 or less or greater than 25µg/L) and then randomized.\textsuperscript{1}

The ITT population had two women discontinue prior to dosing (one from each group), leaving 289 women in the safety population. The results presented were based on the modified intent to treat population (mITT) which included all subjects in the safety population who had at least one Hb reading after baseline. The mITT population was based on 284 women with the exclusion of five women (four IV treatment group and one
oral control group) from the safety population. The ITT population, which included these five women, was re-analyzed and the results were similar to the analysis of the mITT population. The compliance rate of adhering to study protocol treatments was similar in both groups. The investigators indicated there were no differences between treatment groups in the mITT, safety, evaluable, or ITT populations with regards to demographics or hematological parameters with baseline Hb levels of 8.91g/dL and 8.88g/dL and ferritin levels of 24.11µg/L and 23.91µg/L in the IV treatment versus oral groups, respectively.¹

The response of the mITT population that obtained a Hb greater than 12g/dL by the end of the study was significantly greater in the IV ferric carboxymaltose group when compared to the oral iron group (91.4% versus 66.7%, p<0.0001). When looking at the subgroups (stratified by Hb levels) within this population, the subjects with the most severe anemia who received treatment showed the largest difference between the IV treatment versus oral group (78.9% versus 43.5%, p=0.0286) (See Figure 1). The study also examined the percentage of subjects who had an increase in Hb ≥ 3g/dL at any time during the study; a Hb > 12g/dL on or before days 14, 28, and 42; an increase in Hb ≥ 3g/dL on or before days 14, 28, and 42; and time to achieve a Hb greater than 12g/dL. All of these secondary endpoints significantly favored the IV treatment group. The IV treatment group saw a significantly higher percentage of subjects who had an increase in Hb level of 3g/dL or greater (91.4% versus 64.6%, p<0.0001). The results also significantly favored the IV treatment group when looking at length of time to achieve endpoints. a median time to achieve a Hb greater than 12g/dL (14 versus 27 day, p=0.0002) and the median time to achieve an increase in Hb 3g/dL or greater (15 versus
28 days, p<0.0001). Similarly favorable, the ferritin levels of the IV treatment group remained replenished when compared to the control group (238µg/L versus 21µg/L, p<0.0001). Finally, there was a greater significance noted in the percentage of IV treatment group subjects who had a sustained Hb greater than 12g/dL at the end of the study compared to the control group (85.4% versus 58.0%, p<0.0001).1

DISCUSSION

For many pregnant women, postpartum iron deficiency anemia (IDA) is inevitable and can be detrimental to the mother and newborn. After childbirth, it is normal for hemoglobin (Hb) levels to drop during the first 24 hours due to the loss of blood during delivery, however the Hb level should rise over the next two to five days and return to normal by the seventh day after delivery.20 If the Hb level does not rise adequately, postpartum IDA may become a serious problem and may create other problems for the new mother. Studies have shown postpartum women being treated with oral iron when compared to a placebo or non-treatment groups,21 show more rapid Hb increases and correction of anemia with minimal replenishment of iron storage.21,22

Postpartum fatigue and a mother’s declining health have been linked to IDA.17 In addition to fatigue, symptoms of anemia include: inability to concentrate, general apathy, and irritability; all of which can seriously impact a new mother’s quality of life.17 Not surprisingly, all of these factors appear on Beck and Indman’s list of presentations of postpartum depression.23 Studies have shown that treating postpartum IDA with oral iron supplements can improve a mother’s depression and stress scales.9 Therefore, in order to
preclude the onset of postpartum depression, it is extremely important to determine a treatment that reduces recovery time for women with postpartum anemia.

The primary purpose of this systematic review is to determine whether IV iron is a more effective treatment when compared to oral iron therapy in reducing the length of time required to correct postpartum anemia. At first glance, the results of this review appeared to be inconclusive as half of the studies reported significant Hb changes in the IV treatment groups at some point during the study, while the other half reported non-significant results regarding Hb changes. Although, after re-examining each studies inclusion and exclusion criterion, five of the six studies excluded patients requiring blood transfusions, while one of the studies with non-significant results included these patients. Fortunately, the latter study did a sub-analysis, excluding patients who required blood transfusions, thus giving all six studies a common ground to make a viable conclusion about increasing Hb. The results of the sub-analysis in Westad et al revealed a significant change in Hb of at least 2.0g/dL by week four in the treatment group and there was a significant increase in the mean Hb levels of the treatment group at weeks eight and twelve when compared to the oral group. Therefore, four studies showed significant improvements in Hb levels, leaving only two studies with non-significant results, which were conducted by the same author.

Each of the studies except Bhandal et al and Breymann et al, reported a higher percentage of patients who achieved a Hb of greater than 12g/dL at some point during the study using either IV ferric carboxymaltose or IV iron sucrose. However only the studies done by Seid et al, Van Wyck et al, and Westad et al were statistically significant. Although the Bhandal et al study participants did not reach a Hb of 12g/dL, the mean
Hb baseline was 7.4g/dL. Despite the low baseline Hb, the IV group was able to achieve a significant mean Hb increase of 2.5g/dL in the IV group by day five and a statistically significant mean Hb increase of 1.2g/dL in the IV group by day 14. Seid et al\textsuperscript{1} also reported the time to achieve anemia correction was significantly less in the IV treatment group, 14 versus 27 days, while improvements in Hb levels continued for the remainder of the study.

All the studies reported that the IV treatment groups showed a significant elevation in ferritin levels at some point during the testing period. Five of the six studies reported that the ferritin levels remained significantly elevated in the IV treatment groups compared to the oral groups at the termination of each study.\textsuperscript{1,12,14,16,18} Thus, the participants’ iron storage had been replenished more quickly than the participants being treated with oral ferrous sulfate.

Iron status in women of reproductive age significantly affects cognitive performance.\textsuperscript{24} This study also observed association between changes in ferritin and changes in performance, strongly suggesting the brain iron deficiency is causally related to these changes in cognitive performance.\textsuperscript{24} The two studies examined how postpartum anemia affects a mother’s quality of life with both studies showing improvements in both the IV and oral groups with regards to all aspects of the Medical Outcomes Study Short Form 36 (SF-36), although neither was significant. Both studies showed reduction in fatigue; Westad et al\textsuperscript{19} study showed significant improvement in total fatigue at four, eight and twelve weeks in women being treated with IV iron sucrose, while Van Wyck et al\textsuperscript{16} showed no significance between the groups. Since the two studies that looked at maternal quality of life parameters did not have significant results, the actual assessment
tool used to quantify these parameters could have played a role in the lack of significance.

Compliance in each study was, for the most part, fairly high. In the clinical setting it may be difficult to get the same rate of compliance for oral iron therapy as the studies observed because the subjects were willing participants and were given encouragement and reminders by researchers to comply with treatment regimens.

**Study Limitations**

Various limitations plagued the reviewed studies. One limitation is that none of the studies were blinded, thus possibly opening the door for non-study clinicians to be more prone to ordering patients blood transfusions if they were not responding to study treatments, thus requiring these subjects to be excluded. Also, the studies done by Bhandal et al and Breymann et al looked at very small populations of less than 100 subjects, and Breymann et al only studied the participants for a two week time period. Another limitation concerns the process of including or excluding certain individual subjects from the study results. For example, Westad et al had non-significant results when including patients who required blood transfusions, yet had significant results when looking at only patients who did not require blood transfusions.

With the exception of the Seid et al study, which used the methods from the Van Wyck et al, there was little to no uniformity in how the studies were carried out. Treatment administration varied widely among studies. Some studies prescribed iron twice daily while others prescribed thrice daily at various dosages. The studies treating patients with IV iron sucrose also were also inconsistent. The total treatment dosage in these studies ranged from 400mg to 800mg among the treatment
groups. As none of the studies have looked at standard dosage of iron therapy, this would be an excellent topic of further research. Another limitation concerned the times at which the studies drew labs to make their conclusions. For example, Bhandal et al\textsuperscript{14} drew labs five days after baseline, while Westad et al\textsuperscript{19} had the initial hematological parameters drawn at four weeks after baseline. The shorter time interval increases the ability of the researchers to collect important data which could indicate if and when Hb levels returned to normal and how the treatment affected the acute anemia.

CONCLUSION

Both ferric carboxymaltose and iron sucrose are safe and effective ways to treat postpartum iron deficiency anemia. Both forms of intravenous (IV) iron have shorter treatment periods, increased likelihood of compliance, a lack of gastrointestinal side effects, and rapid replenishment of iron stores, making them superior to oral ferrous sulfate. The efficacy of each of the IV iron treatments, iron sucrose and ferric carboxymaltose, have yet to be compared. Future research in this direction would be helpful to guide practitioners in treating their patients with the safest, most effective therapy. Furthermore, the relationship between depleted iron stores and fatigue needs to be explored.\textsuperscript{25} Currently, there are very few studies which examine how anemia affects maternal quality of life parameters. Future research should focus on developing a more effective treatment. An assessment also needs to be made as to how maternal quality of life and postpartum fatigue affect mother-child interaction and child development.
REFERENCES


22. Krafft A, Perewusnyk G, Hanseler E, Quack K, Huch R, Breymann C. Effect of postpartum iron supplementation on red cell and iron parameters in non-anaemic iron-


<table>
<thead>
<tr>
<th>Author/Title/Journal</th>
<th>Yr. published</th>
<th>Patients/Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
<th>Validity (Jadad score)</th>
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<tbody>
<tr>
<td>Bhandal et al\textsuperscript{14}</td>
<td>2006</td>
<td>43 Anemic women (Hb &lt;9g/dL) 24-48 hrs post delivery</td>
<td>IV ferrous sucrose</td>
<td>Oral ferrous sulfate</td>
<td>Hb, ferritin, transferring saturation, red cell indices, transfusions, tolerability to mothers and breast milk sub-study.</td>
<td>RCT</td>
<td>3</td>
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<tr>
<td>Breymann et al\textsuperscript{18}</td>
<td>2000</td>
<td>60 Anemic women (Hb &lt;10g/dL) 24-72 h after delivery</td>
<td>IV ferrous sucrose</td>
<td>Oral ferrous sulfate</td>
<td>Hb, hematocrit, erythropoietin, ferritin, C-Reactive protein</td>
<td>RCT</td>
<td>3</td>
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<tr>
<td>Breymann et al\textsuperscript{12}</td>
<td>2008</td>
<td>268 Anemic women (Hb ≤105g/L) ≤7 days postpartum</td>
<td>IV Ferric Carboxymaltose</td>
<td>Oral ferrous sulfate</td>
<td>Hb, hematocrit, red cell indices, ferritin and serum iron levels measured on baseline, weeks 2, 4, and 12.</td>
<td>RCT</td>
<td>3</td>
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<tr>
<td>Seid et al\textsuperscript{1}</td>
<td>2008</td>
<td>289 Anemic women (Hb ≤10g/dL) ≤10 days postpartum</td>
<td>IV Ferric Carboxymaltose</td>
<td>Oral ferrous sulfate</td>
<td>Correction of anemia, achieving Hb &gt;12g/dL, achieving increase in Hb ≥3g/dL, changes in ferritin and serum transferrin saturation</td>
<td>RCT</td>
<td>3</td>
</tr>
<tr>
<td>Van Wyck et al\textsuperscript{16}</td>
<td>2007</td>
<td>352 Anemic women (Hb ≤10g/dL) ≤10 days postpartum</td>
<td>IV Ferric Carboxymaltose</td>
<td>Oral ferrous sulfate</td>
<td>Correction of anemia</td>
<td>RCT</td>
<td>3</td>
</tr>
<tr>
<td>Westad et al\textsuperscript{19}</td>
<td>2008</td>
<td>128 Postpartum women (Hb ≥6.5g/100ml and ≤8.5g/100ml) ≤48 post delivery</td>
<td>IV ferrous sucrose</td>
<td>Oral ferrous sulfate</td>
<td>Hb, ferritin and quality of life assessed w/ the Medical Outcomes Study Short Form 36 and the Fatigue Scale</td>
<td>RCT</td>
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Table 2: Study Approaches for Dosing Iron Supplementation

<table>
<thead>
<tr>
<th></th>
<th>Intravenous Iron Therapy</th>
<th>Oral Iron Therapy</th>
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<tbody>
<tr>
<td></td>
<td>Ferric Carboxymaltose</td>
<td>Iron Sucrose</td>
</tr>
<tr>
<td>Breymann et al, 2000&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Not given</td>
<td>200mg administered on day 1-4. From day 5 to the end of the study (day 14) subjects were given oral iron supplementation of 80mg iron sulfate plus folic acid (0.35mg) taken twice daily, one hour before meals on an empty stomach</td>
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<tr>
<td></td>
<td></td>
<td>80mg iron sulfate plus folic acid (0.35mg) taken twice daily, one hour before meals on an empty stomach x 14 days</td>
</tr>
<tr>
<td>Bhandal et al, 2006&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Not given</td>
<td>200mg administered in an infusion of 250mL of 0.9% sodium chloride for more than 30 minutes on days 2 and 4</td>
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<tr>
<td></td>
<td></td>
<td>200mg ferrous sulfate, BID x 6 weeks, subjects instructed to take supplement with meal</td>
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<tr>
<td>Westad et al, 2008&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Not given</td>
<td>200mg administered on day 1-3. At the start of week 5, subjects were given oral iron supplementation of 100mg ferrous sulfate twice daily taken twice daily.</td>
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<tr>
<td></td>
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<td>100mg ferrous sulfate, BID x 12 weeks.</td>
</tr>
<tr>
<td>Breymann et al, 2008&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Maximum1000mg over 15 minutes (15mg iron/kg body weight if body weight &lt;66kg) on day 1, subsequent dose at 1 week intervals until patient’s calculated total iron requirement was reached (up to 3 weekly infusions); Calculation for total iron requirement was done by using a modified Ganzoni&lt;sup&gt;26&lt;/sup&gt; formula</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg BID x 12 weeks</td>
</tr>
<tr>
<td>Seid et al, 2008&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Maximum 1000mg over 15 minutes (15mg iron/kg body weight if body weight &lt;66kg) on day 1, subsequent dose at 1 week intervals until patient’s calculated total iron requirement was reached (up to 3 weekly infusions); Maximum total dosage of 2500mg; Calculation for total iron requirement was done by using a modified Ganzoni&lt;sup&gt;26&lt;/sup&gt; formula</td>
<td>Not given</td>
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<tr>
<td></td>
<td></td>
<td>325mg tablets TID for 6 weeks</td>
</tr>
<tr>
<td>Van Wyck et al, 2007&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Maximum 1000mg over 15 minutes (15mg iron/kg body weight if body weight &lt;66kg) on day 1, subsequent dose at 1 week intervals until patient’s calculated total iron requirement was reached (up to 3 weekly infusions); Maximum total dosage of 2500mg; Calculation for total iron requirement was done by using a modified Ganzoni&lt;sup&gt;26&lt;/sup&gt; formula</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>325mg tablets TID with instructions to take 1 tablet by mouth three times daily with 8 ounces of water, one hour before meals on day 0 to 42.</td>
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</table>
Figure 1: Subjects Achieving Correction of Anemia by Baseline Hb in Seid et al\textsuperscript{1} Research.

Percentage of subjects achieving correction of anemia (Hb greater than 12g/dL) by severity of anemia at baseline. The difference in efficacy between ferric carboxymaltose and ferrous sulfate was greater in patients with the most severe anemia

*P = 0.0286, **P = 0.0008, †P = 0.0054, ††P = 0.1000. n/N, number of subjects who achieved a Hb greater than 12g/dL/number of subjects in the treatment group.\textsuperscript{1}