Published in final edited form as:

Am J Obstet Gynecol. 2019 July ; 221(1): 19–29.e3. doi:10.1016/j.ajog.2018.12.016.

Oral versus intravenous iron therapy for postpartum anemia: A systematic review and meta-analysis

P Sultan¹, S Bampoe¹, R Shah², N Guo³, J Estes⁴, C. Stave⁵, L Goodnough⁶, S Halpern⁷, AJ Butwick⁸

¹Consultant Anaesthetist, University College London Hospital

²Specialist Registrar in Anaesthesia, University College London Hospital

³Data Analyst, Stanford University School of Medicine

⁴Resident in Obstetrics and Gynecology, Stanford University School of Medicine

⁵Librarian, Stanford University School of Medicine

⁶Professor of Pathology and Medicine (Hematology), Stanford University

⁷Professor in Anesthesiology, Sunnybrook, Toronto

⁸Associate Professor in Anesthesiology, Stanford University School of Medicine

Abstract

Objective: To perform a systematic review of randomized trials comparing oral versus intravenous iron therapy to treat postpartum anemia.

Data sources: Data sources were: PubMed (1972–2017); Cochrane Central Register of Controlled Trials, CENTRAL (1972–2017); CINAHL (1972–2017); Web of Science; Excerpta Medica Database, and EMBASE (1972–2017).

Study eligibility criteria: We included randomized trials comparing oral versus intravenous iron monotherapy to treat postpartum anemia (classified as a hemoglobin < 12 g/dL).

Study appraisal and synthesis methods: Study quality was assessed with the Cochrane risk of bias assessment tool. The primary outcome was the hemoglobin concentration at 6 weeks postpartum. Secondary outcomes included: hemoglobin concentration at 1 – 5 weeks postpartum, ferritin concentration at 1 – 6 weeks postpartum; and maternal adverse outcomes. For meta-analysis, mean differences and odds ratios using a random effects model were calculated. Risk of heterogeneity was reported as I^2 .

Corresponding author: Dr. Pervez Sultan, Address: University College London Hospital, London, NW1 2BU, p.sultan@doctors.org.uk, Tel: 0845 155 5000.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts:

The authors have no conflicts of interest to declare.

Results: Fifteen randomized trials met our inclusion criteria (n=1,001 and 1,181 women receiving oral iron and intravenous iron, respectively); 4 studies reported data for our primary outcome. We observed higher postpartum week 6 hemoglobin concentrations in the iv iron group compared to the oral iron group, (mean difference 0.9 g/dL, 95% CI=0.4, 1.3; p=0.0003). Compared to oral iron, women receiving iv iron had higher hemoglobin concentrations at postpartum weeks 1, 2, and 3; higher ferritin concentrations at postpartum weeks 1, 2, 4, and 6; an increased likelihood of skin flushing (odds ratio=6.95; 95% confidence interval, 1.56–31.03; P=0.01; I²=0%); and a decreased likelihood of constipation (odds ratio=0.08, 95% confidence interval, 0.03–0.21; P<0.00001, I²=27%) and dyspepsia (odds ratio=0.07, 95% confidence interval, 0.01–0.42; P=0.004; I²=0%). The reported event rate for anaphylaxis among women receiving intravenous iron was 0.6%.

Conclusions: In this systematic review, among women with postpartum anemia, hemoglobin concentrations at 6 weeks postpartum were almost 1 g/dL higher in women who received intravenous iron compared to oral iron. The safety profile of intravenous iron was also reassuring. Given the weaker hemoglobin response and higher risk of gastrointestinal side-effects with oral iron use, our findings suggest that intravenous iron be considered as a viable treatment option for postpartum iron deficiency anemia.

Keywords

Iron; Postpartum Period; Anemia

Introduction

The maternal health burden of postpartum anemia is under-appreciated. Maternal morbidities linked to postpartum anemia include: depression,^{1, 2} fatigue,³ and impaired cognition.⁴ These outcomes can have a negative impact on maternal-child bonding and a mother's ability to care for the neonate.⁵ Given these concerns and that postpartum anemia impacts up to 50% of women in well-resourced countries and up to 80% of women in developing countries,⁶ postpartum anemia is a major and global maternal health problem.

Most women in the developed world with postpartum anemia have antepartum iron deficiency, with iron demands from the developing fetus and with peripartum blood loss further depleting maternal iron reserves.^{6–9} Oral iron is considered the current treatment standard for women with mild-to-moderate iron deficiency postpartum anemia.^{10, 11} However, up to 40% patients are not able to tolerate oral iron due to adverse gastrointestinal effects such as nausea, vomiting, and constipation,¹² resulting in reduced treatment adherence and persistent anemia.¹³ Furthermore, the timing and frequency of oral iron absorption in iron-depleted women can influence fractional iron absorption and dose efficacy.¹⁴ Intravenous (iv) iron may be preferred because the absorption challenges of oral iron are mitigated and iv iron produces a more rapid increase in hemoglobin concentration and iron stores.⁹ Low-molecular weight iron dextran and other formulations also have a reassuring safety record.^{15, 16} Disadvantages of iv iron include increased drug costs and the need for supervised treatment in a hospital or outpatient facility.

In a prior Cochrane review, the effects of iv versus oral iron therapy on maternal fatigue and the risk of maternal death among women with postpartum anemia were examined.¹⁷ However, there were no clear conclusions because fatigue was inconsistently assessed in two studies and only one death was reported which was likely unrelated to iron therapy¹⁸. Importantly, because no postpartum hemoglobin or ferritin indices were reported, the hematological response to iron therapy could not be determined.

Since publication of this review, 4 new randomized trials have been published comparing iv iron to oral iron therapy.^{19–22} Because the findings of newly identified studies can potentially change the conclusions of previous systematic reviews,²³ a comprehensive evaluation of clinical and hematologic data may result in important changes to clinical guidelines and clinical protocols for postpartum anemia management. Therefore, we performed an updated systematic review of all randomized trials with a focus on postpartum hemoglobin as the primary outcome measure.

Objective:

To perform a systematic review of all randomized trials comparing oral versus intravenous (iv) iron therapy to treat postpartum anemia, with postpartum hemoglobin as the primary outcome measure.

Methods

This systematic review was registered with Prospero in November 16th 2017 (registration number CRD42017080234; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=80234) and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁴

Eligibility criteria

We included randomized trials that examined the efficacy of oral versus iv iron therapy for treating postpartum anemia, with no language restriction. Randomized trials of women with a post-delivery hemoglobin level less than 12 g/dL were eligible for our systematic review. Based on anemia criteria in non-pregnant women described by the World Health Organization and Centers for Disease Control and Prevention, we selected a hemoglobin level of 12 g/dL as our cut point for defining postpartum anemia.²⁵ This threshold has been used in prior observational studies of postpartum anemia.^{26, 27} We did not restrict studies based on maternal age, race, pre-existing comorbidities, or mode of delivery. Studies were excluded if iron therapy was administered during the antepartum period. Letters, abstracts, case reports, reviews, comments, editorials, cadaveric studies and animal studies were excluded. We searched the bibliographies of all included studies and relevant review papers for additional trials. For trials with multiple intervention arms, data were extracted comparing groups receiving oral versus iv iron. Because the focus of our review was the effect of iron monotherapy, we did not include studies if other medications, such as folic acid, were co-administered with iron.

Information sources

We performed a literature search without language or date restriction on November 6, 2017 to identify randomized trials comparing the efficacy of oral versus iv iron therapy for treating postpartum anemia. The literature searches included the following terms: iron, postpartum, pregnancy and anemia. Searches were performed in PubMed (includes MEDLINE) (1972–2017); Cochrane Central Register of Controlled Trials, CENTRAL (1972–2017); Cumulative Index to Nursing and Allied Health Literature, CINAHL (1972–2017); Web of Science (see Appendix 1 for specific WOS databases searched); Excerpta Medica Database, EMBASE (1972–2017); and clinicaltrials.gov for unpublished or ongoing studies. Shortlisted articles were entered into the Rayyan reviewing system for systematic reviews online.²⁸

Search strategy

Details of the search criteria used in major databases are provided in Appendix 1. Articles were independently examined by 3 authors (RS, NG, JE) and evaluated for eligibility.

Data extraction

Extracted data included: study country, year, inclusion and exclusion criteria, iron formulation, dosing regimen, duration of study period, primary and secondary outcome data.

The primary outcome was the hemoglobin concentration at 6 weeks postpartum. We selected this outcome for several reasons. First, we are unaware of a validated tool that accurately quantifies postpartum fatigue. Second, the evaluation and management of anemia is a central pillar of patient blood management.²⁹ In obstetrics, the prevention and treatment of postpartum anemia and hematinic deficiencies has been singled out as a key component of patient blood management in obstetrics by the Network for the Advancement in Patient Blood Management, Hemostasis, and Thrombosis (a multidisciplinary panel of experts with an interest in patient blood management).¹¹ Third, assessment of hemoglobin provides an objective measure for assessing the biological response to iron therapy.

Secondary outcomes in our review included: laboratory indices (weekly hemoglobin concentration between 1 week and 5 weeks postpartum; weekly maternal ferritin concentration between 1 week and 6 weeks postpartum), and patient-centric outcomes (maternal fatigue and maternal depression). Specific maternal adverse outcomes and side-effects were also evaluated including: blood transfusion, immune reactions (anaphylaxis, infection, urticaria, flushing, and skin rash), gastrointestinal side-effects (constipation, dyspepsia, muscle cramps, nausea and vomiting), elevation of liver enzymes, and headache.

Assessment of risk of bias

We assessed the quality of studies using the Cochrane Collaboration tool for evaluating the risk of bias.³⁰ Data extraction was independently carried out by five individuals (AB, SB, SH, PS, RS). A standardized collection form was used for data extraction. Discrepancies were resolved by re-examining the original manuscript. If any uncertainty arose, a consensus was obtained among all authors. If study data were presented only in a clear graphical format, the reviewers extracted the data from the relevant graphs. If source data were

unavailable in the published texts, attempts were made to contact the authors to obtain relevant data.

Data synthesis

Quantitative data were analysed using the Review Manager software (RevMan, version 5.3.5; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). For pooled continuous data, mean differences (MDs) with 95% confidence intervals (CIs) were calculated. For pooled dichotomous data, we calculated odds ratios (OR) and 95% CI. Data were analyzed using the DerSimonian random effects model.³¹ We examined statistical heterogeneity using the I^2 statistic. Publication bias was assessed by funnel plot and Egger's test.

Results

Study selection

Figure 1 presents a flow diagram outlining study selection. We identified 32 potential studies for inclusion from the literature search. Fifteen randomized trials met our inclusion criteria. 18–22, 32–41 Reasons for excluding the remaining 17 studies are described in Appendix 2.

Our study cohort comprised 2,182 women, with 1,001 and 1,181 women receiving oral iron and iv iron therapy, respectively. We attempted to contact 4 authors of included studies for additional data,^{33, 38, 39, 41} however none of the contacted authors responded. We found 5 unpublished studies registered on the clinicaltrials.gov website (1/7/2018; supplementary table). Authors were contacted to determine the publication status of these studies; no responses were obtained.

Study characteristics

Study characteristics, including details of iron-dosing regimens, are presented in Table 1. Included studies utilized the following hemoglobin upper limit cut-off values for inclusion criteria: 8 g/dL (4 studies^{34, 35, 37, 38}), 8.5 g/dL (1 study³³), 9 g/dL (3 studies^{20, 32, 41}), 10 g/dL (5 studies^{18, 19, 22, 36, 39}) and 10.5 g/dL (1 study⁴⁰). One study used postpartum hemorrhage as the primary inclusion criteria.²¹ Fourteen trials consisted of 2 treatment arms (oral and iv iron). One study had 3 treatments arms;²² 2 arms comprised iv iron preparations (ferrous sucrose and ferrous carboxymaltose, respectively) and one arm comprised oral iron ascorbate.²² Two studies included women with other co-morbid disease.^{22, 40} One study excluded women with known nutritional disorders.⁴⁰

Risk of bias and publication bias assessment of included studies

Figure 2 summarizes the findings from the risk of bias assessment for included studies. Funnel plot of included studies and Egger's test demonstrated no evidence of publication bias ($p=0.09$; Supplementary Figure).

Synthesis of results

IV iron preparations and dosing regimens—Ferric sucrose was the most common iv iron formulation (9/15 studies).^{20, 22, 32–36, 38, 41} In these studies, the total dose of ferric

sucrose ranged from 300 to 600 mg. Other iv iron formulations studied were: ferric carboxymaltose,^{18, 19, 22, 39, 40} iron dextran,³⁷ and iron maltoside²¹ (Table 1). Among the studies investigating ferric carboxymaltose, the total dose ranged from 1000 to 3000 mg (Table 1). In one study, the total dose of iron dextran was 1000 mg.³⁷ Iron maltosidase was administered as a single dose of 1200 mg in another study.²¹

Oral iron preparations and dosing regimens—Oral iron supplements studied were administered as divalent (ferrous) salts or trivalent (ferric) salts: ferrous sulphate (9 studies^{18, 20, 32–34, 36, 39–41}), ferrous ascarbate (2 studies^{19, 22}), iron protein succinylate (2 studies^{35, 37}) and ferrous fumarate (1 study³⁸). The oral preparation was not described in 1 study.²¹ Oral iron dosing regimens varied. For example, ferrous sulphate doses ranged from 200 mg to 975 mg per day with its duration of treatment ranging from 1 month to 12 weeks.

Patient recruitment and study duration—In 11 studies, patients were recruited within 48 hours of delivery; 2 studies recruited patients up to 10 days following delivery,^{18, 39} and 2 studies did not state the timing of recruitment.^{22, 35} Duration of follow-up varied from 14 days to 12 weeks, with 6 studies describing a 6-week study period.^{18, 19, 22, 36, 37, 39}

Medication adherence—Adherence to a medication regimen was assessed in 10 studies^{18–20, 32, 33, 37–41} but data was only reported in 3 studies.^{18, 19, 32} In 2 studies, adherence was higher in women receiving iv vs. oral iron (98% vs. 84%¹⁸ and 100% vs. 84%¹⁹ respectively). In one study, adherence was equal (100% in both groups³²).

Postpartum hemoglobin and ferritin—In our meta-analysis of 4 studies, the postpartum week 6 hemoglobin concentration was higher in the iv iron group (mean difference = 0.9 g/dL (95 CI=0.4, 1.3; p=0.0003; Figure 3). We observed modest differences in the baseline postpartum hemoglobin concentrations across the 4 studies: 7.4 g/dL,³² 8.8 g/dL¹⁹ 8.5 g/dL²⁰ and 8.1 g/dL.²² In all 4 studies, the mean rise in hemoglobin was higher in the iv iron groups than the oral iron groups (4.2 versus 3.7 g/dL;³² 3.2 versus 2.2 g/dL,¹⁹ 3.0 versus 1.6 g/dL²⁰ and 3.4 versus 2.1 g/dL²²).

For postpartum weeks 1, 2 and 3, hemoglobin concentrations were found to be significantly higher in women receiving iv iron (Table 2). There was a non-significant trend towards a higher hemoglobin concentration at week 4 for women receiving iv iron. No studies reported hemoglobin concentrations at postpartum week 5. We observed high study heterogeneity for all meta-analyses of postpartum hemoglobin by week, with the I^2 statistic ranging from 75%–98%.

Data on between-group differences in postpartum ferritin concentrations (weeks 2, 4, and 6) are presented in (Table 2); no studies assessed ferritin concentrations at weeks 3 or 5. For all weeks, compared to the oral iron group, the iv iron group had statistically significantly higher ferritin concentrations.

Transfusion—Data for postpartum red blood cell transfusion were only reported in two studies.^{21, 33} Because of limited data and information regarding the indications for transfusion, we present transfusion data qualitatively. Holm et al. reported that the rate of

postpartum transfusion was slightly higher in the oral iron group compared to the iv iron group (2% versus 1% respectively).²¹ The transfusion rates reported by Westad et al. were substantially higher in both groups with a more sizeable difference in rates between groups (22.9% versus 8.9%; oral iron versus iv iron, respectively).³³

Fatigue—Three studies reported maternal fatigue. In these studies, fatigue was quantified differently (fatigue linear analog scale¹⁸, a 14-item fatigue scale³³, and a multidimensional fatigue inventory²¹), therefore we report the results qualitatively. In 2 studies, women receiving iv iron had less fatigue than those receiving oral iron. Wested et al. reported that, at 4, 8, and 12 weeks postpartum, women receiving iv iron were less fatigued (relative to baseline) than women receiving oral iron.³³ Holm et al. reported a small but significant decrease in aggregate physical fatigue scores from baseline to 12 weeks postpartum in women receiving iv iron than oral iron.²¹ In contrast, Van Wyck et al. reported that, over the first 42 postpartum days, women receiving iv iron had similar fatigue scores to women receiving oral iron.¹⁸

Depression—Maternal depression was measured in 3 studies,^{18, 21, 33} but data were only reported in 1 study.²¹ In this study, Edinburgh postnatal depression scores were significantly higher in the oral iron group at weeks 1, 3, and 8 postpartum (Appendix 3).²¹ However, these small between-group differences probably have modest clinical significance.

Treatment Related Side-effects—There were no deaths directly attributable to iron therapy. In one study, one patient died of peripartum cardiomyopathy 13 days after vaginal delivery and 7 days after exposure to iv ferric carboxymaltose. Table 3 summarizes the event rates of side-effects among the iv and oral groups. Compared to oral iron, women receiving iv iron also had increased skin flushing (OR=6.95; 95% CI=1.56–31.03) and decreased gastrointestinal related side-effects, notably constipation (OR=0.08 (95% CI=0.03–0.21) and dyspepsia (OR=0.07; 95% CI=0.01–0.42). We observed no statistically significant between-group differences for other side-effects.

Comment

Main findings

In this systematic review and meta-analysis, we examined data from randomized trials comparing iv iron to oral iron in women diagnosed with postpartum anemia. Our main finding is that absolute hemoglobin concentrations at 6 weeks postpartum were almost 1 g/dL higher (equivalent to 1 unit red blood cell transfusion) in women receiving iv compared to oral iron. Similar between-group differences in hemoglobin concentrations were observed at 1, 2, and 3 weeks postpartum. Compared to oral iron, the safety profile of iv iron was reassuring, with women receiving iv iron being at lower risk of gastrointestinal related side-effects. Given the extent of maternal morbidity related to postpartum anemia^{1–5} and the less favorable treatment and side-effect profile of oral iron, our findings suggest that iv iron should be considered as a viable treatment option for postpartum iron deficiency anemia.

Strengths and limitations

Our study has several limitations. Our main findings are limited by the degree of heterogeneity between trials. This heterogeneity may be due to differences in mode of delivery, iron formulations, doses, dosing frequency, duration of drug exposure, baseline hemoglobin and iron status of study patients, and other unreported differences between study groups. There were insufficient data to perform sensitivity analyses because only 4 studies reported hemoglobin concentrations at week 6 postpartum. While the effect size was heterogeneous, all 4 studies reported that the mean rise in hemoglobin (from baseline to 6 weeks postpartum) was higher with iv iron compared to oral iron. The methodological quality of many included studies was not high, with only a minority of studies having a low risk of bias in most domains. Of note, there was a high or unclear risk of bias related to blinding of the participants in all studies. Primary and secondary outcomes were not consistently reported in included studies. For example, dyspepsia was only reported in 3 studies. This may explain the low level of precision (wide confidence intervals) of the odds ratios for dyspepsia and other iron-related side-effects and complications. Due to the extent of study heterogeneity, we did not examine cost or perform cost-effectiveness analysis for different iron formulations. However, iv iron formulations that rapidly restore body iron stores with fewer infusions are likely to be associated with decreased hospital resource utilization and lower costs compared to iv iron regimens requiring multiple infusions.⁴² Potentially important patient-centric outcomes, such as cognition and executive decision-making,^{4, 43, 44} were not examined. These measures may be more sensitive to changes in iron status than fatigue and depression. Further research is needed to evaluate the potential impact of iv and oral iron therapy on these outcome measures. Twelve studies included women that had undergone a variety of delivery modes (delivery mode data was not presented in 3 studies). None of the included studies performed analysis of iv versus oral iron therapy according to mode of delivery, therefore precluding subgroup analysis in our review.

Finally, for our primary outcome (hemoglobin concentration at 6 weeks postpartum), only 4 studies reported data, with baseline hemoglobin values ranging from 7.4 – 8.1 g/dL. Therefore, it is uncertain whether the responses to iv or oral iron differ in women with baseline hemoglobin concentrations outside of this range. Further studies are needed to examine the most appropriate cutoffs for hemoglobin concentration and indicators of iron status for initiating postpartum iron therapy. These studies should take into account the range of values associated with optimal maternal outcomes in the postpartum period.

Comparison to existing literature

To our knowledge, only one prior systematic (Cochrane) review has examined the effectiveness and safety of iv versus oral iron in postpartum women.¹⁷ In this review, postpartum fatigue and maternal death were the primary outcomes. However, no clear conclusions were reported. Our updated review is larger than the Cochrane review, with 5 additional studies, yielding an analysis of 15 studies in over 2100 patients. In our systematic review, few studies report clinical or patient-centric outcomes therefore we could only analyze these outcomes qualitatively. Nonetheless, our findings suggest that, compared to iv iron, women receiving oral iron may experience a higher rate of transfusion, and a greater

degree of maternal fatigue and depression. We accept that other biological, social, and economic factors (such as sleep deprivation, pain, depression) can impact postpartum fatigue.⁴⁵ These factors may mask any potential effect of iron deficiency on postpartum fatigue. A separate meta-analysis of 29 obstetric and non-obstetric studies reported no deaths related to iv iron.¹⁵ Therefore it appears unlikely that a significant difference exists in the risk of death between oral iron versus iv iron formulations.

In light of the aforementioned challenges in differentiating the effect of iv versus oral iron on patient-centric outcomes, we selected postpartum hemoglobin as our primary outcome. Other reasons also justify our choice of primary outcome. By examining hemoglobin concentrations up to 6 weeks postpartum, we could objectively quantify the hematological response to oral and iv iron therapy. Monitoring hemoglobin concentrations has clinical importance because limiting anemia and the use of inappropriate RBC transfusions are central components of patient blood management.²⁹ In the non-obstetric literature, there is an expanding body of evidence indicating that implementation of patient blood management practices reduces transfusion needs, perioperative morbidity, length of stay, and costs.⁴⁶ Our main finding that the hemoglobin concentration at 6 weeks was nearly 1 g/dL higher in the iv iron group compared to the oral group is clinically relevant because an equivalent rise in haemoglobin concentration is observed after a 1 unit RBC transfusion.^{47–49} Therefore, any risk associated with transfusion before hospital discharge may be lowered commensurately if iv iron is considered as an alternate treatment modality to oral iron.

Our main findings are likely explained by the fact that iv iron produces a greater rate of increase in body iron stores than oral iron. Consistent with our findings, a prior review has highlighted a number of non-obstetric studies that report a greater rise in hemoglobin concentration and iron stores over a shorter period with iv iron compared with oral iron.¹² The ferritin concentrations of women receiving iv iron were also significantly higher in women receiving iv compared to oral iron. This observation may be explained by the fact that ferritin concentrations from week 1 postpartum are more likely influenced by body iron status than any residual inflammatory effects related to delivery.⁶ The comparatively lower ferritin and hemoglobin concentrations in women treated with oral iron may be due to reduced gastrointestinal absorption and poorer patient compliance due to gastrointestinal side-effects.⁵⁰ The majority of studies utilized 2 or 3 times daily oral iron dosing. This is of clinical relevance because acute, consecutive-day oral iron administration has been shown to increase circulating plasma hepcidin which, secondarily, down-regulates intestinal iron absorption resulting in decreased iron bioavailability.¹⁴ Future studies are needed to determine whether increasing the dosing interval between successive oral iron doses improves iron bioavailability, reduces gastrointestinal side-effects and improves patient compliance among women with postpartum anemia.

In our analysis, iv iron was associated with a lower risk of gastrointestinal side-effects compared with oral iron. Compared with oral iron, women had a significantly lower odds of constipation (OR=0.08; 95% CI=0.03–31 and dyspepsia (OR=0.08; 95% CI=0.01–42). Our findings are similar to those of a prior meta-analysis of obstetric and non-obstetric studies in which oral iron (ferrous sulphate) was associated with a 3-fold increased odds of gastrointestinal side-effects compared to iv iron.⁵¹ Apart from flushing, iv iron was not

associated with a higher risk of side-effects compared to oral iron. Consistent with our findings, a meta-analysis by Avni et al. also reported no increase in adverse events including: cardiovascular, neurological, thromboembolic or gastrointestinal events, and infections, in patients receiving iv iron therapy compared with those receiving oral, intramuscular iron, no iron, or placebo.¹⁵ Reassuringly, we only identified 2 cases of possible anaphylaxis to iv iron. Avni et al. reported no episodes of anaphylaxis or death after iv iron exposure but did report an increased risk of infusion reaction.¹⁵ In our analysis, features of hypersensitivity reactions, namely urticaria and rash, occurred rarely following iv iron exposure (0.6% and 4.6%, respectively). Despite the rarity of hypersensitivity reactions following iv iron, the Network for the Advancement in Patient Blood Management, Hemostasis, and Thrombosis recommend that staff who administer iv iron should be familiar with approaches to prevent and manage these adverse reactions.¹¹

Current guidelines for postpartum anemia management recommend that iv iron be considered only after a failed trial of oral iron (secondary to an inadequate hemoglobin response or patient intolerance to oral iron.)¹¹ However, in the non-obstetric literature, there is increasing interest in the use of iv iron for the primary treatment of severe iron deficiency anemia.^{50, 52} Given the greater rise in hemoglobin concentration and favorable side-effect profile of iv iron, our findings may help inform future guidelines for postpartum anemia management. Our findings are also consistent with those from a recent meta-analysis comparing iv versus oral iron for antepartum anemia treatment.⁵³ Since postpartum iron deficiency anemia is often preceded by antepartum anemia,^{6, 7} adequate identification and treatment of antepartum anemia may help reduce the prevalence or severity of postpartum anemia and the subsequent need for postpartum iron therapy.

Conclusions and implications

In conclusion, our meta-analysis shows that, compared to oral iron, iv iron is associated with higher hemoglobin concentrations in the first 6 weeks postpartum and a lower risk of gastrointestinal side-effects in patients with postpartum anemia. These findings may inform future guidelines and recommendations for the treatment of postpartum anemia due to iron deficiency. Comparative effectiveness and cost-effectiveness studies are necessary to further justify any changes in current clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Dr. Butwick is supported by an award from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (1K23HD070972). Dr. Bampoe is supported by an award from the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Appendix 1.: Bibliographic database search strategies

PUBMED

("Ferric Compounds" [mesh] OR "Iron-Dextran Complex" [mesh] OR Iron [tw] OR ferric* [tw] OR ferrous* [tw] OR Venofer [tw]) AND ("pregnancy" [mesh] OR gravida* [ti] OR "lactation" [mesh] OR "breast feeding"[mesh] OR "breast feeding" [tw] OR postpartum [tw] OR "Postpartum Period" [mesh] OR puerperal [tw] OR pregnan* [tw] OR maternal [tw] OR lactat* [tw]) AND (anemic* [tw] OR anemia* [tw] OR anaemia* [tw] OR "Anemia, Iron-Deficiency" [mesh] OR "Postpartum Hemorrhage" [mesh] OR (postpartum [ti] AND hemorr* [ti])) AND (random*[tw] OR placebo*[ti] OR "double blind"[tw] OR blinded[tw] OR "single blind"[tw] OR controlled clinical trial[pt] OR controls[ti] OR control[ti] OR controlled [ti] OR trial [ti] OR trials [ti] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square"[tw] OR randomized controlled trial[pt] OR "Clinical Trials as Topic" [mesh]) AND english [lang] NOT ("animals" [mesh] NOT "humans" [mesh])

EMBASE

('ferric carboxymaltose'/exp OR 'iron therapy':de OR 'antienemic agent' OR iron:ti,ab,kw,de OR ferric*:ti,ab,kw,de OR ferrous*:ti,ab,kw,de OR venofer:ti,ab,kw,de) AND ('pregnant woman':de OR 'breast feeding':ti,ab,kw,de OR pregnan*:ti,ab,kw,de OR 'puerperium'/exp OR gravida*:ti OR lactation:de OR postpartum:ti,ab,kw,de OR puerperal:ti,ab,kw,de OR pregnan*:ti,ab,kw,de OR maternal:ti,ab,kw,de OR lactat*:ti,ab,kw,de) AND (anemic*:ti,ab,kw,de OR anemia*:ti,ab,kw,de OR anaemia*:ti,ab,kw,de OR 'iron deficiency':ti,kw,ab,de OR 'anemia'/exp OR 'postpartum hemorrhage'/exp OR 'postpartum hemorrhage':ti,kw,ab,de) AND (random*:ti,ab,kw,de OR placebo*:ti OR 'double blind':ti,ab,kw,de OR blinded:ti,ab,kw,de OR 'single blind':ti,ab,kw,de OR ((singl*:ti,ab,kw,de OR doubl*:ti,ab,kw,de OR trebl*:ti,ab,kw,de OR tripl*:ti,ab,kw,de) AND (mask*:ti,ab,kw,de OR blind*:ti,ab,kw,de)) OR 'latin square':ti,ab,kw,de OR 'randomized controlled trial'/exp OR control*:ti OR 'controlled clinical trial'/exp OR trial*:ti) AND [english]/lim

COCHRANE LIBRARY

(Iron OR ferric* OR ferrous* OR Venofer) AND (pregnan* OR gravida* OR lactat* OR postpartum OR puerperal OR maternal) AND (anemic* OR anemia* OR anaemia* OR "Postpartum Hemorrhage")

CLINICALTRIALS.GOV

(Iron OR ferric* OR ferrous* OR Venofer) AND (pregnan* OR gravida* OR lactat* OR postpartum OR puerperal OR maternal) AND (anemic* OR anemia* OR anaemia* OR "Postpartum Hemorrhage")

WEB OF SCIENCE:

WOS databases included: Science Citation Index Expanded; Conference Proceedings Citation Index – Science; Conference Proceedings Citation Index – Social Science & Humanities; Emerging Sources Citation Index)

TITLE: ((pregnan* OR gravida* OR lactat* OR postpartum OR puerperal OR maternal))

AND TITLE: ((Iron OR ferric* OR ferrous* OR Venofer)) **AND TOPIC:** ((anemic* OR anemia* OR anaemia* OR Postpartum Hemorrhage))

Appendix 2.: Studies excluded at eligibility phase of search

- 1.⁵⁴ Abstract for 2008 Seid et al. study³⁹
- 2.⁵⁵ Abstract for the 2008 Westad et al. study³³
- 3.⁵⁶ Not a randomized trial.
- 4.⁵⁷ Not a randomized trial.
- 5.⁵⁸ Study protocol.
- 6.⁵⁹ Letter.
- 7.⁶⁰ Letter.
- 8.⁶¹ Conference abstract.
- 9.⁶² Antenatal anemia and iron therapy.
- 10.⁶³ Outcomes do not meet inclusion criteria. No baseline hemoglobin, no continuous postpartum data reported.
- 11.⁶⁴ Not a randomized controlled trial.
- 12.⁶⁵ Abstract with no continuous data, only conclusion from 2 studies presented.
- 13.⁶⁶ Non-randomized study
- 14.⁶⁷ Not stated if study was randomized
- 15.⁶⁸ Quasirandomization. Allocation of group not clear.
- 16.⁶⁹ Folic acid co-administered with iron therapy
- 17.⁷⁰ Folic acid co-administered with iron therapy

Appendix 3.: Evaluation of depression

Time of assessment	Mean Depression Score (SE) ²¹	
	Oral Iron (EDPS)	Intravenous Iron (EDPS)
Baseline	Not reported	Not reported
7 days	8 (7.5–8.4)	5.7 (5.3–6.0)
21 days	6 (5.5–6.4)	4.7 (4.3–5.2)
56 days	4.6 (4.3–4.9)	3.3 (2.9–3.7)
84 days	3.7 (3.4–4.2)	2.9 (2.5–3.2)

EDPS=Edinburgh postnatal depression score; The maximum score is 30, and a score 10 indicates possible depression; measured in this study at the following time points: postoperative day 7, 21, 56 and 84 days

References

1. Gaynes BN, Gavin N, Meltzer-Brody S, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. *Evid Rep Technol Assess (Summ)* 2005;1–8.
2. Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for postpartum depression. *J Nutr* 2003;133:4139–42. [PubMed: 14652362]
3. Lee KA, Zaffke ME. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. *J Obstet Gynecol Neonatal Nurs* 1999;28:183–91.
4. Beard J, Hendricks M, Perez E, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition *J Nutr* 2005;135:267–72. [PubMed: 15671224]
5. Murray-Kolb LE, Beard JL. Iron deficiency and child and maternal health. *Am J Clin Nutr* 2009;89:946s–50s. [PubMed: 19158210]
6. MILMAN N Postpartum anemia I: definition, prevalence, causes, and consequences. *Ann Hematol* 2011;90:1247–53. [PubMed: 21710167]
7. Butwick AJ, Walsh EM, Kuzniewicz M, Li SX, Escobar GJ. Patterns and predictors of severe postpartum anemia after Cesarean section. *Transfusion* 2017;57:36–44. [PubMed: 27618767]
8. Wagner KS, Ronsmans C, Thomas SL, et al. Women who experience obstetric haemorrhage are at higher risk of anaemia, in both rich and poor countries. *Trop Med Int Health* 2012;17:9–22. [PubMed: 21955293]
9. Milman N Postpartum anemia II: prevention and treatment. *Ann Hematol* 2012;91:143–54. [PubMed: 22160256]
10. WHO Guideline: Iron supplementation in postpartum women. Geneva: World Health Organization, 2016 URL: <http://apps.who.int/iris/handle/10665/249242>. Accessed August 15th, 2018.
11. Munoz M, Pena-Rosas JP, Robinson S, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. *Transfus Med* 2018;28:22–39. [PubMed: 28722245]
12. Friedman AJ, Shander A, Martin SR, et al. Iron deficiency anemia in women: a practical guide to detection, diagnosis, and treatment. *Obstet Gynecol Surv* 2015;70:342–53. [PubMed: 25974731]
13. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. *Am J Clin Nutr* 2015;102:1585–94. [PubMed: 26561626]
14. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* 2015;126:1981–9. [PubMed: 26289639]
15. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clin Proc* 2015;90:12–23. [PubMed: 25572192]

16. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2016;387:907–16. [PubMed: 26314490]
17. Markova V, Norgaard A, Jorgensen KJ, Langhoff-Roos J. Treatment for women with postpartum iron deficiency anaemia. *The Cochrane database of systematic reviews* 2015;Cd010861. [PubMed: 26270434]
18. Van Wyck DB, Martens MG, Seid MH, Baker JB, Mangione A. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. *Obstet Gynecol* 2007;110:267–78. [PubMed: 17666600]
19. Damineni S, Thunga S. IV ferric carboxymaltose vs oral iron in the treatment of post-partum iron deficiency anaemia. *J Clin Diag Res* 2016;10:QC08–10.
20. El Khouly NI. Comparison of intravenous ferrous sucrose and oral ferrous sulphate in treatment of postpartum iron deficiency anemia. *J Matern Fetal Neonatal Med* 2017;30:967–71. [PubMed: 27269410]
21. Holm C, Thomsen L, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial. *Vox Sang* 2017;112:219–28. [PubMed: 28198084]
22. Rathod S, Samal SK, Mahapatra PC, Samal S. Ferric carboxymaltose: A revolution in the treatment of postpartum anemia in Indian women. *Int J Appl Basic Med Res* 2015;5:25–30. [PubMed: 25664264]
23. Garner P, Hopewell S, Chandler J, et al. When and how to update systematic reviews: consensus and checklist. *BMJ* 2016;354:i3507. [PubMed: 27443385]
24. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41. [PubMed: 20171303]
25. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recommendations and reports* 1998;47:1–29.
26. Bodnar LM, Scanlon KS, Freedman DS, Siega-Riz AM, Cogswell ME. High prevalence of postpartum anemia among low-income women in the United States. *Am J Obstet Gynecol* 2001;185:438–43. [PubMed: 11518906]
27. Bodnar LM, Siega-Riz AM, Miller WC, Cogswell ME, McDonald T. Who should be screened for postpartum anemia? An evaluation of current recommendations. *Am J Epidemiol* 2002;156:903–12. [PubMed: 12419762]
28. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210. [PubMed: 27919275]
29. Goodnough LT, Shander A. Patient blood management. *Anesthesiology* 2012;116:1367–76. [PubMed: 22487863]
30. Higgins JPT, Altman DG, Sterne JAC. *Cochrane handbook for systematic reviews of interventions* vsn 5.1.0. The Cochrane Collaboration, 2011 URL: <https://training.cochrane.org/handbook>. Accessed August 18th, 2018.
31. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88. [PubMed: 3802833]
32. Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. *BJOG* 2006;113:1248–52. [PubMed: 17004982]
33. Westad S, Backe B, Salvesen K, et al. A 12-week randomised study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anemia. *Acta Obst Gynecol Scand* 2008; 87:916–23. [PubMed: 18720044]
34. Verma S, Inamdar S, Malhotra N. Intravenous iron therapy versus oral iron in postpartum patients in rural area. *J S Asian Fed Obstet Gynaecol* 2011;3:67–70.
35. Giannoulis C, Daniilidis A, Tantanasis T, Dinas K, Tzafettas J. Intravenous administration of iron sucrose for treating anemia in postpartum women. *Hippokratia* 2009;13:38–40. [PubMed: 19240819]
36. Guerra MS, Lopez PA, Munoz HH, Marin MJ, Lete LI, Aizpuru BF. Randomized clinical trial to evaluate the effectiveness of two routes of iron administration, oral and intravenous, in the treatment of postpartum iron deficiency anemia. *Clin Invest Gyna Obst* 2012;39:190–95.

37. Daniilidis A, Giannoulis C, Pantelis A, Tantanasis T, Dinas K. Total infusion of low molecular weight iron-dextran for treating postpartum anemia. *Clin Exp Obstet Gynecol* 2011;38:159–61. [PubMed: 21793279]
38. Jain G, Palaria U, Jha S. Intravenous iron in postpartum anemia. *Journal Obst Gynaecol India* 2013;63:45–48.
39. Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, Rogers R. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. *Am J Obstet Gynecol* 2008;199:435.e1–7. [PubMed: 18928998]
40. Breymann C, Gliga F, Bejenariu C, Strizhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. *Int J Gynaecol Obstet* 2008;101:67–73. [PubMed: 18234203]
41. Mumtaz A, Farooq F. Comparison for effects of intravenous versus oral iron therapy for postpartum anemia. *Pak J Med and Health Sci* 2011;5:116–20.
42. Pollock RF, Muduma G. A budget impact analysis of parenteral iron treatments for iron deficiency anemia in the UK: reduced resource utilization with iron isomaltoside 1000. *Clinicoecon Outcomes Res* 2017;9:475–83. [PubMed: 28848355]
43. Blanton CA, Green MW, Kretsch MJ. Body iron is associated with cognitive executive planning function in college women. *The Br J Nutr* 2013;109:906–13. [PubMed: 22676919]
44. Scott SP, Murray-Kolb LE. Iron Status Is Associated with Performance on Executive Functioning Tasks in Nonanemic Young Women. *J Nutr* 2016;146:30–7. [PubMed: 26661838]
45. Troy NW. Is the significance of postpartum fatigue being overlooked in the lives of women? *MCN Am J Matern Child Nurs* 2003;28:252–7; quiz 58–9. [PubMed: 12840692]
46. Shander A, Isbister J, Gombotz H. Patient blood management: the global view. *Transfusion* 2016;56:S94–102. [PubMed: 27001367]
47. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med* 1992;116:393–402. [PubMed: 1736773]
48. Goodnough LT, Bravo JR, Hsueh YS, Keating LJ, Brittenham GM. Red blood cell mass in autologous and homologous blood units. Implications for risk/benefit assessment of autologous blood crossover and directed blood transfusion. *Transfusion* 1989;29:821–2. [PubMed: 2588319]
49. Goodnough LT, Levy JH, Murphy MF. Concepts of blood transfusion in adults. *Lancet* 2013;381:1845–54. [PubMed: 23706801]
50. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010;116:4754–61. [PubMed: 20826717]
51. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PloS one* 2015;10:e0117383. [PubMed: 25700159]
52. Camaschella C New insights into iron deficiency and iron deficiency anemia. *Blood Rev* 2017;31:225–33. [PubMed: 28216263]
53. Govindappagari S, Burwick RM. Treatment of Iron Deficiency Anemia in Pregnancy with Intravenous versus Oral Iron: Systematic Review and Meta-Analysis. *Am J Perinatol* 2018 [Epub ahead of print].
54. Seid M, Rogers R, Dinh Q. Treating postpartum anemia with intravenous ferric carboxymaltose in a randomized controlled study. *Am J Obstet Gynecol* 2007;197:S26, Abstract no:55. [PubMed: 17825647]
55. Westad S, Backe B, Salvesen K, Nakling J, Okland I, Borthen I. A 12-week randomised, multi-centre study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anaemia. *Int J Gynaecol and Obstet*, 2009;107:S377.
56. Agrawal S Is intravenous iron sucrose an alternative to the oral iron-folate supplementation for treating iron deficiency anemia in pregnant and post natal women. *Int J Gynecol Obstet* 2012;119:S268–S69.
57. Amrita C, Neha S, Veena G, Beenu. A prospective study comparing the efficacy of oral iron, intravenous Ironsucrose and Ferric-carboxy-maltose in postpartum anemia. *Int J Med Res Health Sci* 2016;5:107–11.

58. Holm C, Thomsen L, Norgaard A, Langhoff-Roos J. Intravenous iron isomaltoside 1000 administered by high single-dose infusions or standard medical care for the treatment of fatigue in women after postpartum haemorrhage: study protocol for a randomised controlled trial. *Trials* 2015;16:5. [PubMed: 25588587]
59. Jatoth P, Coundjidapadam CS. Intravenous versus oral iron therapy for postpartum anaemia. *BJOG* 2007;114:655. [PubMed: 17439582]
60. Urato AC. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. *Obstet Gynecol* 2008;112:703.
61. Holm C, Thomsen L, Norgaard A, Langhoff-Roos J. Intravenous iron isomaltoside 1000 (monofer) administered by a high single-dose infusion or standard medical care for the treatment of fatigue in women after postpartum haemorrhage: a randomized controlled trial. *Int J Gynecol Obstet* 2015;131:E118.
62. Khalafallah A, Dennis A, Ogden K, et al. Three-year follow-up of a randomised clinical trial of intravenous versus oral iron for anaemia in pregnancy. *BMJ open* 2012;2:5.
63. Razzaq M, Azam MI, Naeem MF. Comparison between intravenous iron and oral iron therapy in cases of postpartum anemia. *Pak J Med Health Sci* 2017;11:277–80.
64. Vijayalakshmi S, Mahendra G, Pukale RS, Linthoingambi R. Intravenous iron versus oral iron therapy in postpartum anaemia in rural india. *J Evolution Med Dental Sci* 2015;4:1666–71.
65. Holm C. Intravenous iron treatment after postpartum haemorrhage. *Transfusion Medicine* 2016;26:23.
66. Kaur P, Kaur G, Bhatia R, Singh J, Aggarwal T, Kaur P. To study the comparison of oral iron versus parenteral iron sucrose in the treatment of postpartum anaemia. *J Evol Med Dental Sci* 2017;6:5337–39.
67. Dede A, Uygur D, Yilmaz B, Mungan T, Ugur M. Intravenous iron sucrose complex vs. oral ferrous sulfate for postpartum iron deficiency anemia. *Int J Gynaecol Obstet* 2005;90:238–9. [PubMed: 16043181]
68. Pradhan S, Patel O, Raju MD, Dash P. study of oral versus intravenous iron therapy in postpartum anaemic women. *J Evol Med Dental Sci* 2017;6:4101–06.
69. Froessler B, Cocchiari C, Saadat-Gilani K, Hodyl N, Dekker G. Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: a randomized trial. *J Matern Fetal Neonatal Med* 2013;26:654–9. [PubMed: 23130909]
70. Iyoke CA, Emegoakor FC, Ezugwu EC, et al. Effect of treatment with single total-dose intravenous iron versus daily oral iron(III)-hydroxide polymaltose on moderate puerperal iron-deficiency anemia. *Ther Clin Risk Manag* 2017;13:647–53. [PubMed: 28761350]

Condensation:

Women with postpartum anemia treated with intravenous iron have postpartum week 6 hemoglobin concentrations nearly 1 g/dL higher than those treated with oral iron.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

AJOG at a Glance:

- It is uncertain whether oral iron or intravenous iron should be the primary treatment modality for women with postpartum iron-deficiency anemia.
- Compared with oral iron, women receiving intravenous iron had higher hemoglobin concentrations at week 6 postpartum and a lower risk of gastrointestinal side-effects.
- Findings from this systematic review and meta-analysis suggest that iv iron is a viable treatment option for postpartum iron-deficiency anemia.

Figure 1. Prisma flowchart for studies identified and excluded (included studies 18–22, 32–41)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bhandal 2006	+	+	-	+	+	+	?
Breymann 2008	+	-	-	-	+	?	?
Damineni 2016	?	-	-	-	+	+	-
Daniilidis 2011	?	-	-	-	+	+	?
El Khoully 2017	+	+	-	+	+	+	?
Giannoulis 2009	?	-	-	-	+	?	-
Guerra 2012	?	?	-	?	+	+	-
Holm 2017	+	+	-	+	+	?	?
Jain 2013	+	-	-	+	+	+	?
Mumtaz 2011	?	-	?	?	?	+	?
Rathod 2015	?	-	-	-	?	?	?
Seid 2008	+	+	-	+	+	+	?
Van Wyck 2007	+	+	-	+	+	+	?
Verma 2011	?	-	-	-	-	-	?
Westad 2008	+	+	-	+	+	+	?

Figure 2. Risk of bias assessment of included studies

- =High risk of bias

? = unclear risk of bias

+ = Low risk of bias

Figure 3. Forest plot for the mean difference in hemoglobin at 6 weeks postpartum

CI, confidence intervals; IV, inverse variance; random, random effects model; SD, standard deviation

Table 1.

Characteristics of included studies

First Author Year Country	IV iron n Oral iron n	IV iron formulation Oral iron formulation	IV iron dosing regimen Oral iron dosing regimen	IV iron total dose PO iron total daily dose	IV iron (alternate / weekly PO iron (duration of exposure)	Period of patient recruitment	Study duration
Bhandal ³² 2006 UK	22	Ferrous sucrose	200 mg on D2 and D4	400mg	Alternate	24 – 48 h post delivery	40 days
	21	Ferrous sulphate	200 mg bd	400mg	6 weeks		
Jain ³⁸ 2013 India	21	Ferrous sucrose	100–200 mg 3 times / wk *	300–600 mg	Alternate	24 – 48 h post delivery	14 days
	20	Ferrous fumarate	300 mg od	300mg	14 days		
Seid ³⁹ 2008 USA	138	Ferric carboxymaltose	15 mg/kg not exceeding 1000 mg. If total calculated dose >1000 mg, subsequent doses administered weekly until total dose received (up to maximum 2500 mg)	Up to 2500 mg	Weekly	<10 days post delivery	42 days
	144	Ferrous sulphate	325 mg tds	975 mg	6 weeks		
Van Wyck ¹⁸ 2007 USA	168	Ferric carboxymaltose	15 mg/kg not exceeding 1000 mg. If total calculated dose >1000 mg, subsequent doses administered weekly until total dose received (up to maximum 2500 mg)	Up to 2500 mg	Weekly	<10 days post delivery	42 days
	169	Ferrous sulphate	325 mg tds	975 mg	6 weeks		
Westad ³³ 2008 Norway	45	Ferrous sucrose	200 mg daily for 3 days	600 mg	Consecutive	<48 h post delivery	84 days
	48	Ferrous sulphate	100 mg bd	200 mg	12 weeks		
Verma ³⁴ 2011 India	75	Ferric sucrose	200 mg daily for 3 days	600 mg	Consecutive	After 24 h post delivery	30 days
	75	Ferrous sulphate	200 mg bd	400 mg	1 month		
Breymann ⁴⁰ 2008 Romania [#]	179	Ferric carboxymaltose	Up to a maximum of 3 weekly doses of 1000 mg	Up to 3000 mg	Weekly	Within 12 weeks of delivery	84 days
	89	Ferrous sulphate	100 mg bd (total based on modified formula of Ganzoni)	200 mg	12 weeks		
Damineni ¹⁹ 2016 India	45	Ferric carboxymaltose	1000 mg single dose	1000 mg	Single dose	24 h post delivery	42 days
	45	Ferrous ascorbate	100 mg bd	200 mg	6 weeks		
El khoully ²⁰ 2017 Egypt	162	Ferrous sucrose	Iron dose calculated* and administered in 3 divided doses on D1, 3 and 5	Maximum dose not stated	Alternate	<48 h post delivery	40 days

First Author Year Country	IV iron n Oral iron n	IV iron formulation Oral iron formulation	IV iron dosing regimen Oral iron dosing regimen	IV iron total dose PO iron total daily dose	IV iron (alternate / consecutive days / weekly PO iron (duration of exposure)	Period of patient recruitment	Study duration
	154	Ferrous sulphate	150 mg bd	300mg	6 weeks		
Giannoulis ³⁵ 2009 Greece	52 20	Ferrous sucrose Iron protein succinylate	100 mg daily for 3 days 800 mg od	300 mg 800 mg	Consecutive 1 month	Post delivery (timing not stated)	28 days
Guerra ³⁶ 2012 Spain	6 7	Ferrous sucrose Ferrous sulphate	2 doses 200 mg on D2 and D4 post delivery 200 mg bd	400 mg 400 mg	Alternate 6 weeks	D1 post delivery	42 days
Holm ²¹ 2017 Denmark	97 99	Iron maltoside Not stated	1200 mg single dose 40–50mg daily, or 100 mg od or bd for a variable time period according to Danish Health authority	1200 mg 100 – 200 mg	Single dose Not stated	D1 post delivery	84 days
Mumtaz ⁴¹ 2011 Pakistan	40 40	Ferrous sucrose Ferrous sulphate	200 mg on D2 and D4 (dose based on pooled data from different studies) 200 mg bd	400 mg 400 mg	Alternate 6 weeks	24–48 h post delivery	40 days
Daniilidis ³⁷ 2011 Greece	109 26	Iron dextran Iron protein succinylate	500 mg daily infusion for 2 days 800 mg od for 6 weeks	1000 mg 800 mg	Consecutive 6 weeks	Day of delivery	42 days
Rathod ²² 2015 India	22 14 30	Ferrous sucrose Ferrous carboxymaltose Iron ascorbate	If <66 kg calculated cumulative dose was rounded down to nearest 100 mg. If >66 kg cumulative dose was rounded upto the nearest 100 mg. 15 mg/kg BW (maximum single dose 1000 mg no greater than once weekly and not exceeding 15 mg iron/kg or calculated cumulative dose) 100 mg od for 6 weeks	Maximum total dose not stated Not stated 100mg	Maximum doses not stated Not stated 6 weeks	Post delivery (timing not stated)	42 days

PO=oral; h=hour; D=postpartum day; alternate days = D1, 3, 5, etc.; consecutive days = D1, 2, 3 etc.;

* total iron dose in mg = $2.4 \times W \times \text{deficit}$, where W is the body weight in kg, deficit = target Hb – actual Hb in g%;

= multicentre trial in Romania, Switzerland and Russia;

od=once daily; bd=twice daily; tds=three times daily; Hb =hemoglobin concentration

Table 2.

Postpartum hemoglobin and ferritin concentrations

	Postpartum Week	Number of studies	Number of patients (iv)	Number of patients (oral)	Mean Difference [95% confidence intervals]	Higher in iv or Oral	P-value	I ² (%)
Hemoglobin (g/dL)	1	11	724	512	1.0 [0.5, 1.5]	iv	<0.0001	98
	2	7	543	437	1.2 [0.5, 1.9]	iv	0.0007	98
	3	2	172	174	1.3 [0.06, 2.6]	iv	0.04	75
	4	4	351	232	0.7 [-0.3, 1.6]	ND	0.18	97
	6	4	251	134	0.9 [0.4, 1.3]	iv	0.0003	78
Ferritin (ng/mL)	1	8	667	456	181.47 [163.94, 198.99]	iv	<0.00001	100
	2	7	528	440	201.82 [148.89, 254.75]	iv	<0.00001	100
	4	5	482	282	136.32 [44.71, 227.92]	iv	0.004	99
	6	4	427	437	31.60 [29.56, 33.63]	iv	<0.00001	100

ND=no difference between groups

Table 3.

Iron-related side-effects and complications

Side-effect	Number of studies	Number of events / patients		Odds Ratio	P-value	I ²
		Oral Iron	IV Iron			
Flushing	4	0/107	15/174	6.95 [1.56, 31.03]	0.01	0
Constipation	8	79/667	7/868	0.08 [0.03, 0.21]	<0.00001	27
Dyspepsia	3	7/100	0/204	0.07 [0.01, 0.42]	0.004	0
Nausea	6	25/430	13/525	0.52 [0.13, 1.98]	0.33	51
Muscle cramps	2	–04	5/203	3.85 [0.62, 23.98]	0.15	0
ALT rise	2	9/362	6/467	0.46 [0.09, 2.23]	0.33	38
AST rise	1	3/245	–40	0.34 [0.03, 3.31]	0.35	N/A*
Headache	6	8/508	25/707	2.06 [0.95, 4.43]	0.07	0
Anaphylaxis	4	0/161	1/163	3.04 [0.12, 75.83]	0.50	N/A*
Urticaria	2	1/167	4/163	4.23 [0.47, 38.33]	0.2	N/A*
Rash	2	4/198	9/195	2.37 [0.72, 7.85]	0.16	N/A*
Infection	3	22/359	25/357	1.16 [0.63, 2.13]	0.64	0

ALT = alanine transferase; AST= aspartate transaminase; IV = intravenous; N/A*= reported events from 1 study so I² not possible