Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis

Pervez Sultan, FRCA; Sohail Bampoe, FRCA; Raj Shah, FRCA; Nan Guo, PhD; Jaclyn Estes, MD; Christopher Stave, MLS; Lawrence Tim Goodnough, MD; Stephen Halpern, FRCPC; Alex James Butwick, FRCA

OBJECTIVE: To perform a systematic review of randomized trials comparing oral vs intravenous (IV) iron therapy to treat postpartum anemia.

DATA SOURCES: Data sources were as follows: 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 vs IV 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 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.

RESULTS: A total of 15 randomized trials met our inclusion criteria (n = 1001 and 1 181 women receiving oral iron and IV 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% confidence interval (CI), 0.4–1.3; $P = .0003$). 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 [OR], 6.95; 95% CI, 1.56–31.03; $P = .01$; $I^2 = 0\%$); and a decreased likelihood of constipation (OR, 0.08; 95% CI, 0.03–0.21; $P < .00001$, $I^2 = 27\%$) and dyspepsia (OR, 0.07; 95% confidence interval, 0.01–0.42; $P = .004$; $I^2 = 0\%$). The reported event rate for anaphylaxis among women receiving IV iron was 0.6%.

CONCLUSION: 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 IV iron compared to oral iron. The safety profile of IV iron was also reassuring. Given the weaker hemoglobin response and higher risk of gastrointestinal side effects with oral iron use, our findings suggest that IV iron be considered as a viable treatment option for postpartum iron deficiency anemia.

Key words: anemia, iron, postpartum period

Introduction

The maternal health burden of postpartum anemia is underappreciated. 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 affects 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% of 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 because 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 vs 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

From the University College London Hospital (Drs Sultan, Bampoe, Shah), London, UK; Stanford University School of Medicine (Drs Guo, Estes, Stave, Goodnough, and Butwick), Stanford, CA; and Department of Anesthesia, Sunnybrook Health Sciences (Dr Halpern), Toronto, ON, Canada.

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Corresponding author: Pervez Sultan. p.sultan@doctors.org.uk

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AJOG at a Glance

Why was this study conducted?

It is uncertain whether oral iron or intravenous iron should be the primary treatment modality for women with postpartum iron-deficiency anemia.

Key findings

Compared with oral iron, women receiving intravenous iron had higher hemoglobin concentrations at week 6 postpartum and a lower risk of gastrointestinal side effects.

What does this add to what is known?

Findings from this systematic review and meta-analysis suggest that IV iron is a viable treatment option for postpartum iron-deficiency anemia.

inconsistently assessed in 2 studies and only 1 death was reported, which was likely unrelated to iron therapy.[18] Importantly, because no postpartum hemoglobin or ferritin indices were reported, the hematological response to iron therapy could not be determined.

Since the publication of that 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 comparing oral vs IV iron therapy to treat postpartum anemia, with postpartum hemoglobin as the primary outcome measure.

Materials and Methods

This systematic review was registered with Prospero in November 16, 2017 (registration number CRD42017080234; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=80234) and was 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 vs IV iron therapy for treating postpartum anemia, with no language restriction. Randomized trials of women with a postdelivery hemoglobin level of <12 g/dL were eligible for our systematic review. Based on anemia criteria in nonpregnant women described by the World Health Organization and the 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 vs 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 vs 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 Web of Science 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 (R.S., N.G., J.E.) and evaluated for eligibility.

Data extraction

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

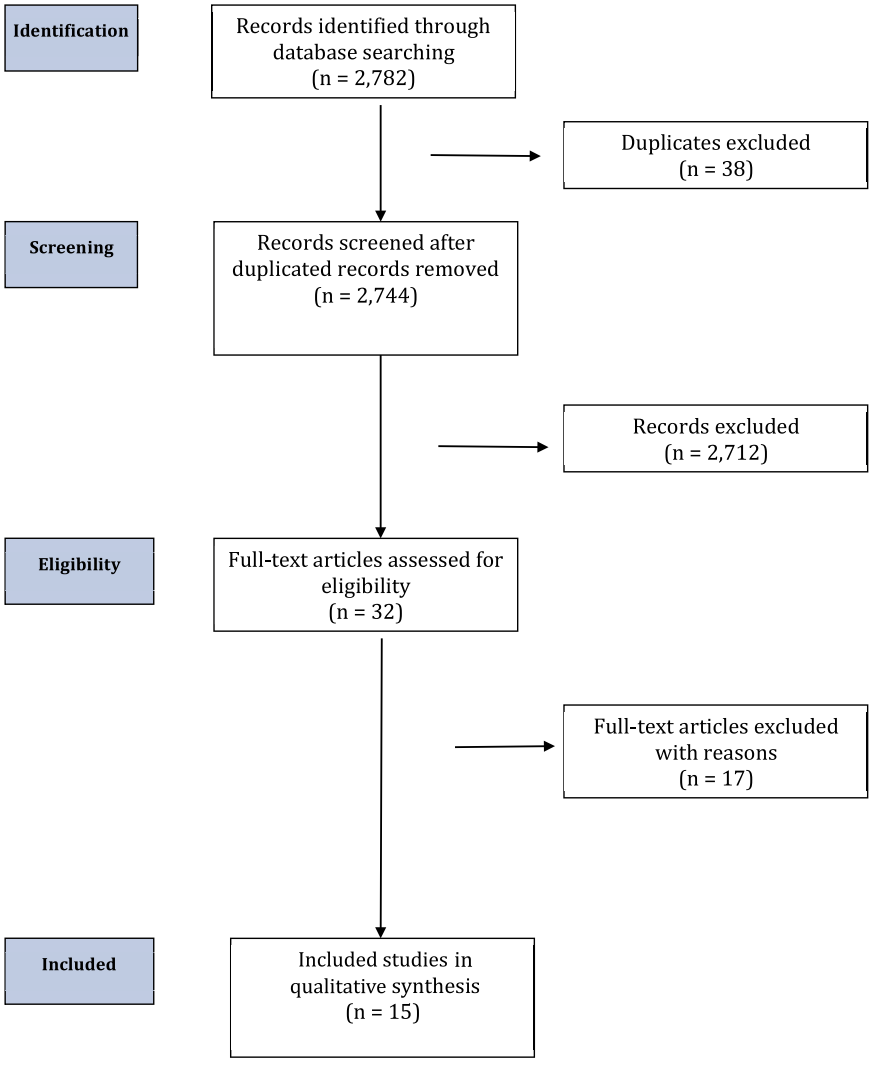
Assessment of risk of bias

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 5 individuals (A.B., S.B., S.H., P.S., R.S.). 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 analyzed using the Review Manager software (RevMan, version 5.3.5; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). For pooled continuous data, mean differences with 95% confidence intervals (CIs) were calculated. For pooled dichotomous data, we calculated odds ratios (OR) and 95% CIs. 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 test.

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for studies identified and excluded (included studies[18-22,32-41])



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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 2182 women, with 1001 and 1181 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 (Jan. 7, 2018) (Supplementary Table 1). 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 used 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 study[33]), 9 g/dL (3 studies[20,32,41]), 10 g/dL (5 studies[18,19,22,36,39]) and 10.5 g/dL (1 study[40]). One study used postpartum hemorrhage as the primary inclusion criterion.[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 1 arm comprised oral

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 Oral iron total daily dose	IV Iron (alternate / consecutive days / weekly) Oral iron (duration of exposure)	Period of patient recruitment	Study duration
Bhandal[32] 2006 UK	22 21	Ferrous sucrose Ferrous sulphate	200 mg on D2 and D4 200 mg bd	400 mg 400 mg	Alternate 6 wk	24–48 h post delivery	40 days
Jain[38] 2013 India	21 20	Ferrous sucrose Ferrous fumarate	100–200 mg 3 times/wk[a] 300 mg od	300–600 mg 300 mg	Alternate 14 days	24–48 h post delivery	14 days
Seid[39] 2008 USA	138 144	Ferric carboxymaltose Ferrous sulphate	15 mg/kg not exceeding 1000 mg. If total calculated dose is >1000 mg, subsequent doses administered weekly until total dose received (up to maximum 2500 mg) 325 mg tds	Up to 2500 mg 975 mg	Weekly 6 wk	<10 days post delivery	42 days
Van Wyck[18] 2007 USA	168 169	Ferric carboxymaltose Ferrous sulphate	15 mg/kg not exceeding 1000 mg. If total calculated dose is >1000 mg, subsequent doses administered weekly until total dose received (up to maximum 2500 mg) 325 mg tds	Up to 2500 mg 975 mg	Weekly 6 wk	<10 days post delivery	42 days
Westad[33] 2008 Norway	45 48	Ferrous sucrose Ferrous sulphate	200 mg daily for 3 days 100 mg bd	600 mg 200 mg	Consecutive 12 wk	<48 h post delivery	84 days
Verma[34] 2011 India	75 75	Ferric sucrose Ferrous sulphate	200 mg daily for 3 days 200 mg bd	600 mg 400 mg	Consecutive 1 mo	After 24 h post delivery	30 days
Breymann[40] 2008 Romania[b]	179 89	Ferric carboxymaltose Ferrous sulphate	Up to a maximum of 3 weekly doses of 1000 mg 100 mg bd (total based on modified formula of Ganzomi)	Up to 3000 mg 200 mg	Weekly 12 wk	Within 12 wk of delivery	84 days
Damineni[19] 2016 India	45 45	Ferric carboxymaltose Ferrous ascarbate	1000 mg single dose 100 mg bd	1000 mg 200 mg	Single dose 6 wk	24 h post delivery	42 days
El khouly[20] 2017 Egypt	162 154	Ferrous sucrose Ferrous sulphate	Iron dose calculated* and administered in 3 divided doses on D1, 3 and 5 150 mg bd	Maximum dose not stated 300 mg	Alternate 6 wk	<48 h post delivery	40 days
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 mo	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 wk	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

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TABLE 1
Characteristics of included studies *(continued)*

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 Oral iron total daily dose	IV Iron (alternate / consecutive days / weekly) Oral iron (duration of exposure)	Period of patient recruitment	Study duration
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 wk	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 wk	1000 mg 800 mg	Consecutive 6 wk	Day of delivery	42 days
Rathod[22] 2015 India	22 14 30	Ferrous sucrose Ferrous carboxymaltose Iron ascarbate	If <66 kg, calculated cumulative dose was rounded down to nearest 100 mg. If >66 kg, cumulative dose was rounded up to 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 wk	Maximum total dose not stated Not stated 100 mg	Maximum doses not stated Not stated 6 wk	Post delivery (timing not stated)	42 days

Alternate days, D1, 3, 5, etc.; *bd,* Twice daily; *BW,* body weight; consecutive days, D1, 2, 3 etc.; *D,* postpartum day; *h,* hour; *Hb,* hemoglobin concentration; *IV,* intravenous; *mo,* month; *od,* once daily; *PO,* oral; *tds,* 3 times daily.

[a] Total iron dose in mg = 2.4 × W × deficit, where W is the body weight in kg, deficit = target Hb − actual Hb in g%; [b] Multicenter trial in Romania, Switzerland, and Russia.

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iron ascarbate.[22] Two studies included women with other comorbid 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 the Egger test demonstrated no evidence of publication bias ($P = .09$) (Figure 3).

Synthesis of results

Intravenous iron preparations and dosing regimens. Ferric sucrose was the most common IV iron formulation (9 of 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 maltoside[21] (Table 1). Among the studies investigating ferric carboxymaltose, the total dose ranged from 1000 to 3000 mg (Table 1). In 1 study, the total dose of iron dextran was 1000 mg.[37] In another study, iron maltosidase was administered as a single dose of 1200 mg.[21]

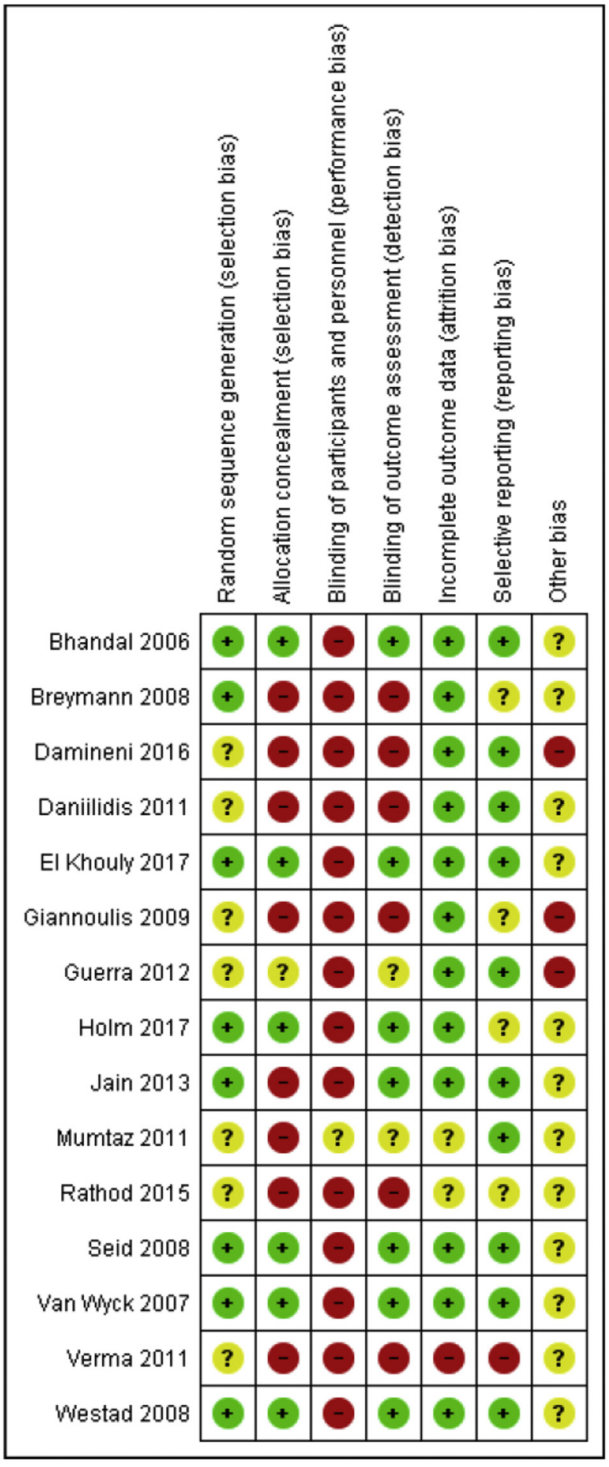
Oral iron preparations and dosing regimens. Oral iron supplements studied were administered as divalent (ferrous) salts or trivalent (ferric) salts: ferrous sulphate (9 studies[18,20,32-34,36,39-41]), ferrous ascarbate (2 studies[19,22]), iron protein succinylate (2 studies[35,37]) and ferrous fumarate (1 study[38]). 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 their 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 were reported in only 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 1 study, adherence was equal (100% in both groups[32]).

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; $P = .0003$) (Figure 4). We observed modest differences in the

FIGURE 2
Risk of bias assessment of included studies



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baseline postpartum hemoglobin concentrations across the 4 studies: 7.4 g/dL,[32] 8.8 g/dL,[19] 8.5 g/dL,[20] 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 vs 3.7 g/dL,[32] 3.2 vs 2.2 g/dL,[19] 3.0 vs 1.6 g/dL,[20] and 3.4 vs 2.1 g/dL[22]).

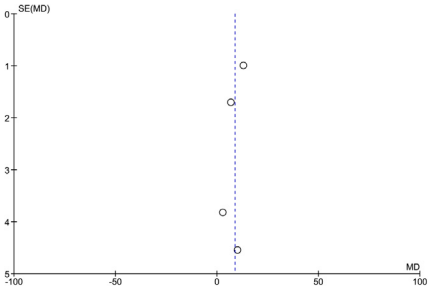
For postpartum weeks 1, 2 and 3, hemoglobin concentrations were found to be significantly higher in women receiving IV iron (Table 2). There was a nonsignificant trend toward a higher hemoglobin concentration at week 4 for women receiving IV iron. No studies reported hemoglobin concentrations at postpartum week 5. We observed high study heterogeneity for all meta-analyses of postpartum hemoglobin by week, with the I^2 statistic ranging from 75% to 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 reported in only 2 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% vs 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% vs 8.9% for oral iron vs IV iron, respectively).[33]

Fatigue. Three studies reported maternal fatigue. In these studies, fatigue was quantified differently (fatigue linear analog scale,[18] a 14-item fatigue scale,[33] and a multidimensional fatigue inventory[21]); therefore we report the results qualitatively. In 2 studies, women receiving IV iron had less fatigue than those receiving oral iron. Wested et al

FIGURE 3
Funnel plot of included studies



SE (MD), standard error (mean difference); *MD*, mean difference.

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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 compared with those receiving oral iron.[21] In contrast, Van Wyck et al reported that over the first 42 postpartum days, women receiving IV iron had fatigue scores similar to those of women receiving oral iron.[18]

Depression. Maternal depression was measured in 3 studies,[18,21,33] but data were reported only 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 (Supplementary Table 2).[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 1 study, 1 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 (odds ratio [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

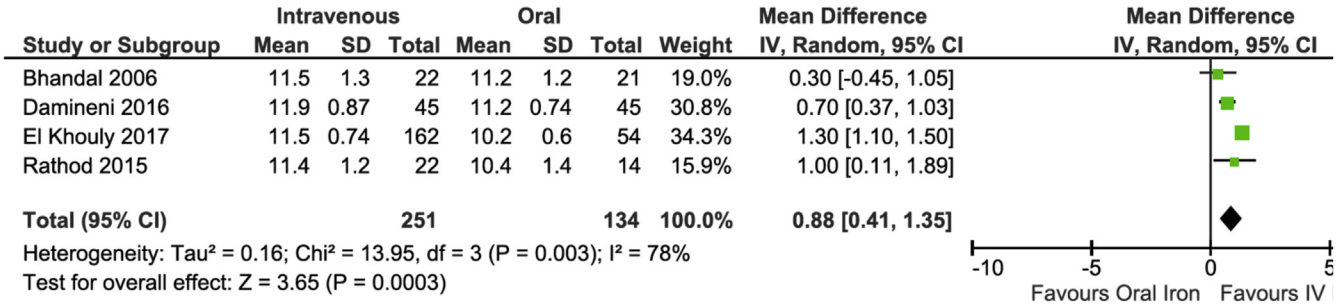
Main findings

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 for 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. Although 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

FIGURE 4
Forest plot for the mean difference in hemoglobin at 6 weeks postpartum



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

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TABLE 2
Postpartum hemoglobin and ferritin concentrations

	Postpartum week	Number of studies	Number of patients (IV)	Number of patients (oral)	Mean difference (95% confidence interval)	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 to 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; *IV,* intravenous.

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reported in only 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. Because of 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 use 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 were not presented in 3 studies). None of the included studies performed analysis of IV vs 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 to 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.

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)	.01	0
Constipation	8	79/667	7/868	0.08 (0.03–0.21)	<.00001	27
Dyspepsia	3	7/100	0/204	0.07 (0.01–0.42)	.004	0
Nausea	6	25/430	13/525	0.52 (0.13–1.98)	.33	51
Muscle cramps	2	1/204	5/203	3.85 (0.62–23.98)	.15	0
ALT rise	2	9/362	6/467	0.46 (0.09–2.23)	.33	38
AST rise	1	3/245	1/240	0.34 (0.03–3.31)	.35	N/A
Headache	6	8/508	25/707	2.06 (0.95–4.43)	.07	0
Anaphylaxis	4	0/161	1/163	3.04 (0.12–75.83)	.50	N/A
Urticaria	2	1/167	4/163	4.23 (0.47–38.33)	.2	N/A
Rash	2	4/198	9/195	2.37 (0.72–7.85)	.16	N/A
Infection	3	22/359	25/357	1.16 (0.63–2.13)	.64	0

ALT, alanine transferase; *AST,* aspartate transaminase; *IV,* intravenous; *N/A,* not applicable.

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Comparison to existing literature

To our knowledge, only 1 prior systematic (Cochrane) review has examined the effectiveness and safety of IV vs 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 more than 2100 patients. In our systematic review, few studies report clinical or patient-centric outcomes; therefore, we could analyze these outcomes only 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, and depression) can have an impact on postpartum fatigue.[45] These factors may mask any potential effect of iron deficiency on postpartum fatigue. A separate meta-analysis of 29 obstetric and nonobstetric 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 vs IV iron formulations.

In light of the aforementioned challenges in differentiating the effect of IV vs 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 nonobstetric 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 1g/dL higher in the IV iron group compared to the oral iron group is clinically relevant, because an equivalent rise in hemoglobin concentration is observed after a 1-unit red blood cell transfusion.[47-49] Therefore, any risk associated with transfusion before hospital discharge may be lowered commensurately if IV iron is considered as an alternative 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 nonobstetric 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 because of gastrointestinal side effects.[50] The majority of studies used 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 hepicidin, which secondarily downregulates 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 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 nonobstetric 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 patients receiving oral iron, intramuscular iron, no iron, or placebo.[15] It was reassuring that we identified only 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 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 nonobstetric 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 vs oral iron for antepartum anemia treatment.[53] Because 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. ■

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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 pregan*: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 defficiency':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 study[39]
2. [55] Abstract for the 2008 Westad et al study[33]
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 conclusions from 2 studies presented.
13. [66] Nonrandomized study
14. [67] Not stated whether 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

SUPPLEMENTARY TABLE 1
Unpublished studies on clinicaltrials.gov website

Author, year of registry	Oral preparation IV Preparation	Primary outcome	Secondary outcomes	Completion status	Response from author (yes/no)
Yefet, Israel, 2015	Iron bisglycinate Ferrous sucrose	Change in Hb from baseline to 6 wk postpartum	Change in Hb from baseline to 3 wk postpartum Women's satisfaction (based on VAS) after 3 and 6 wk postpartum Composite symptoms (anemia and functional capacity) after 3 and 6 wk postpartum as assessed by a questionnaire Adherence at 6 wk postpartum Change in ferritin, serum iron, transferrin, MCV, iron saturation, and reticulocytes count at 3 and 6 wk postpartum Number of women reaching a target Hb of >12 g/dL after 6 wk of treatment	Recruiting	No
Backe, 2009	Ferrous sulphate Ferric carboxymaltose	Hb concentration at 6 wk postpartum	Ferritin at 6 wk postpartum Fatigue at 6 wk postpartum Quality of life at 6 wk postpartum Postpartum depression at 6 wk postpartum	Terminated	No
Hossain, 2012	Ferrous sulphate Iron isomaltoside	Time for Hb to rise by ≥2g/dL	Hb at 2 wk and 3 mo postpartum	Completed	No
Luitpold Pharmaceuticals, 2006	Ferrous sulphate Ferric carboxymaltose	Number of subjects achieving ≥2.0 g/dL increase in Hb	Not stated	Completed	No
Luitpold Pharmaceuticals, 2006	Ferrous sulphate Ferric carboxymaltose	Number of patients achieving Hb >12 g/dL	Not stated	Completed	No

Hb, hemoglobin concentration; *IV,* intravenous; *MCV,* mean corpuscular volume; *VAS,* visual analogue scale.

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SUPPLEMENTARY TABLE 2
Evaluation of depression

	Mean depression score (SE)[21]	
Time of assessment	**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 of ≥10 indicates possible depression; measured in this study at the following time points: postoperative days 7, 21, 56, and 84.

Sultan. Iron and postpartum anemia. Am J Obstet Gynecol 2019.