

Iron Therapy for Heavy Menstrual Bleeding Related Iron Deficiency Anaemia: Efficacy, Tolerability and Evidence Gaps for Women with Diabetes Mellitus. A Systematic Review

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Systematic Review

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Abstract

Background

Heavy menstrual bleeding is a leading cause of iron deficiency anaemia, and comparative evidence on iron therapy is fragmented across administration routes and formulations. We assessed the efficacy, tolerability and treatment burden of iron therapy for anaemia related to heavy menstrual bleeding, its applicability to women with diabetes mellitus, and the implications for clinical care.

Methods

MEDLINE, Embase, CENTRAL, CINAHL, Scopus, Web of Science and Google Scholar were searched on 18 and 19 August 2026 for reports from 2000 onwards, without language restriction. Randomised and quasi randomised trials comparing iron therapy with any other intervention were eligible. Risk of bias was assessed with RoB 2 and certainty with GRADE. Comparable outcomes were pooled in a random effects model and others synthesised narratively. Diabetes status and glycated haemoglobin outcomes were examined.

Results

Of 736 records, 178 duplicates were removed and 558 were screened. Of 80 reports sought, 27 could not be retrieved and 53 were assessed; 11 were excluded, leaving 42 reports of 13 studies. Of these, 2 compared intravenous with oral iron, 6 compared intravenous formulations, 2 compared intravenous iron with placebo or standard care and 3 assessed adjunctive interventions. Both route comparison trials, published in 2009, showed faster haematological correction with intravenous iron (low certainty). Head to head intravenous comparisons showed broadly similar later haemoglobin responses (moderate certainty) but differences in the number of administrations and in phosphate related safety. For ferric carboxymaltose against iron sucrose at 12 weeks, 2 trials with 118 analysed participants gave a pooled mean difference of -0.00 g/dL (95% confidence interval -0.32 to 0.31 ; I^2 23%; low certainty). One trial reported 1 participant with diabetes in each arm, and no trial reported diabetes stratified treatment effects or change in glycated haemoglobin.

Conclusions

Intravenous iron corrected anaemia faster than oral iron in 2 older trials, and later haemoglobin responses across intravenous preparations were broadly similar. Treatment choice should consider tolerance, attendance burden, preparation specific safety and follow up, not haemoglobin response alone. Comparative evidence for women with diabetes is lacking.

Systematic review registration:

PROSPERO CRD420261449093.

Background

Heavy menstrual bleeding (HMB) affects a large proportion of women during their reproductive years and is the main cause of iron deficiency anaemia (IDA) in this group [1]. Its consequences extend beyond a low haemoglobin concentration to fatigue, reduced work and academic performance, impaired cognitive function and reduced quality of life. Because these effects accumulate over time and are not resolved by a single course of treatment, iron replacement remains the main management strategy, supplemented by interventions that address the bleeding itself. Standard treatments to reduce blood loss include the levonorgestrel releasing intrauterine system, combined hormonal contraception, progestogens and tranexamic acid. These therapies act as cointerventions and need to be considered in any trial of iron therapy in this population. Over the past 2 decades, the therapeutic debate has centred on oral iron, which is inexpensive and widely available but often poorly tolerated [2] and slowly absorbed, and intravenous (IV) iron, which corrects anaemia and replenishes iron stores rapidly but requires infusion resources and carries preparation specific risks [3].

A reassessment of this framework is needed for 2 reasons. First, the number of licensed IV iron preparations has increased, and these differ in the maximum dose per infusion, the number of clinic visits required and the incidence of hypophosphataemia [3, 4]. Repeated hypophosphataemia can lead to skeletal complications such as osteomalacia and fractures [5, 6]. Second, the burden on health services, measured by the number of infusions and clinic visits, has become a critical consideration, especially where infusion capacity is limited.

Diabetes mellitus adds further clinical complexity. Iron deficiency and its correction can alter measured glycated haemoglobin (HbA1c) independently of actual glycaemic control [7, 8]. Women with both diabetes and HMB may therefore have their glycaemic status misinterpreted before and after iron therapy, with a risk of inappropriate changes to diabetes management based on measurement artefacts. The comparative efficacy, tolerability and safety of iron therapies in this subgroup, and the extent to which iron repletion systematically affects measured HbA1c, remain unestablished.

Relevance to women's health care

Care for women with heavy menstrual bleeding and anaemia involves gynaecologists, general practitioners, midwives and nurses, who contribute to recognising menstrual blood loss and symptoms of anaemia, supporting adherence to prescribed oral iron, delivering IV treatment within local protocols, documenting adverse effects and arranging follow up. Comparative evidence on the speed of correction, the number of treatment visits, fatigue and formulation specific safety is therefore relevant to clinical assessment, patient education and coordinated care [9, 10, 11, 12, 13, 14]. For women with diabetes, the relevance extends to communicating iron status when HbA1c is interpreted [7, 8].

Rationale

Evidence specific to HMB is dispersed across trials comparing administration routes, IV preparations and adjunctive interventions [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. A focused synthesis is needed to

distinguish these comparisons, assess treatment burden and preparation specific safety, and establish whether the evidence informs care for women with diabetes mellitus.

This review synthesises randomised evidence on iron therapy for IDA resulting from HMB across all relevant comparisons. It evaluates efficacy, safety and the number of administrations required, and assesses whether trials report data relevant to interpreting HbA1c after iron repletion. The findings are intended to guide clinicians caring for women in choosing between oral and IV iron, and among IV preparations, in settings with differing infusion capacity, and to identify evidence gaps for women with diabetes that future trials should address.

Objectives

The primary objective was to compare the effect of iron therapy on haemoglobin concentration in non pregnant females of reproductive age with IDA related to HMB, assessed at the end of the treatment period and, where reported, at 8 to 12 weeks.

The secondary objectives were (1) to compare the safety, tolerability and treatment burden of the iron therapies compared, including adverse events, treatment discontinuation and the number of administrations; (2) to compare secondary haematological and patient centred outcomes, including anaemia resolution, iron status markers, time to response, fatigue and health related quality of life; and (3) to assess the effect of iron replacement on HbA1c and evaluate the applicability of the evidence to women with diabetes mellitus.

Methods

Protocol and registration

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [22]. The narrative synthesis is reported according to the Synthesis Without Meta-analysis (SWiM) guideline [23], and methodological decisions were guided by the Cochrane Handbook for Systematic Reviews of Interventions, version 6.5 [24]. The protocol was registered prospectively in PROSPERO (CRD420261449093). The registered protocol required diabetes mellitus, an IV against oral comparison, publication from 2010 onwards and haemoglobin assessment at 8 to 12 weeks. During study selection it became clear that these criteria would yield no diabetes specific trial and would exclude both direct route comparison trials identified by the search. The protocol was therefore amended (version 1.1, 22 August 2026) before the final synthesis. The amendments, their timing, rationale and consequences are described under Protocol amendments after registration.

Eligibility criteria

Eligibility criteria were prespecified in the registered protocol and, as amended, are set out in full in Table 1.

Table 1
Eligibility criteria

Domain	Included	Excluded
Population	Females of reproductive age from menarche onwards with iron deficiency anaemia attributable to heavy menstrual bleeding or abnormal uterine bleeding, as defined by the International Federation of Gynecology and Obstetrics systems [25]. Populations of mixed aetiology were eligible where a bleeding subgroup was extractable	Pregnancy, the postpartum period, anaemia attributable to causes other than bleeding, males, and populations defined by another condition such as chronic kidney disease or inflammatory bowel disease
Intervention	Any iron therapy by any route, preparation, dose or schedule	Interventions that are not iron therapy
Comparator	Any other intervention, including a different iron preparation, route, dose or schedule, placebo, no treatment, or iron combined with another agent	Single arm studies with no comparator
Outcomes	Eligible irrespective of the outcomes reported, provided an extractable haemoglobin outcome was available	No extractable haemoglobin outcome
Design	Randomised and quasi randomised controlled trials, including parallel group, cluster randomised, crossover and multi arm designs	Observational, cohort, case control and cross sectional studies, case series, surveys, reviews, and protocols without outcome data

Information sources and search strategy

We searched MEDLINE and Embase via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost, Scopus, Web of Science Core Collection and Google Scholar. All searches were completed on 18 and 19 August 2026, with MEDLINE covering 1946 to 14 August 2026 and Embase 1974 to 13 August 2026. The strategy combined controlled vocabulary and free text terms for heavy menstrual bleeding, abnormal uterine bleeding, iron deficiency, IDA and iron therapy, with truncation and proximity operators where appropriate, and applied a filter for randomised, quasi randomised and controlled trials. Retrieval was restricted to reports published from 2000 onwards. No diabetes or route of administration terms were included, so the search covered the amended eligibility criteria. An experienced health sciences information specialist developed the strategy and adapted it to the syntax of each database. No language restriction was applied at the search or screening stage, and all studies meeting the criteria were reported in English. We also searched trial registries for ongoing and unpublished studies and screened the reference lists of relevant studies by hand. The full search strategy for each source, including the trial filter and date limit, is provided in Additional file 1.

Study selection

Records were imported into EPPI-Reviewer (EPPI Centre, UCL Social Research Institute, University College London, United Kingdom) [26], which was used for reference management, duplicate removal, title and abstract screening, full text assessment and documentation of selection decisions. Every screening decision was recorded in the review database, together with the reason for exclusion at the full text stage.

Potential duplicates were identified with the automatic duplicate detection function of EPPI-Reviewer, and 1 reviewer (G.K.) verified each flagged pair manually before removal. Duplicate removal was treated as a reference management step rather than an eligibility decision. No other automated function was used during study selection: priority screening, study classifiers, term recognition and other text mining or machine learning tools were not used to rank, include or exclude records. A human reviewer assessed every title, abstract and full text report, and no record was excluded through an automated process.

All titles and abstracts were screened against the eligibility criteria by 2 reviewers (G.K. and A.A.K.) working independently, who then independently assessed the full text of each potentially eligible report. Each reviewer was blinded to the other's decisions until both had completed the stage. The 2 sets of decisions were compared at each stage and disagreements were resolved by discussion; where consensus could not be reached, a third reviewer (F.K. or M.S.) arbitrated. Records whose eligibility could not be determined from the title and abstract were carried forward to full text assessment.

Companion reports, conference abstracts, corrections, extension studies and trial registrations were linked to their parent study so that each study was counted once, and the number of reports contributing to each study was recorded. The flow of records through identification, screening and inclusion, with reasons for exclusion at the full text stage, is shown in Fig. 1.

Figure 1 PRISMA 2020 flow diagram of study selection

Records were identified from 6 bibliographic databases and Google Scholar. Reasons for exclusion at full text: wrong population ($n = 2$), not a randomised comparative trial ($n = 6$), eligible subgroup data not extractable ($n = 1$), not a primary comparative study ($n = 1$) and intervention not iron therapy ($n = 1$). Layout adapted from the PRISMA 2020 flow diagram for databases and registers [22].

Data collection

G.K. extracted data from all 13 included studies before the final synthesis. The extraction form recorded study characteristics, setting, participants, interventions and comparators (including preparation and cumulative dose), all prespecified outcomes, funding sources and author affiliations. After the review began, the form was expanded to capture hypophosphataemia, adverse events by type (gastrointestinal intolerance, hypersensitivity and infusion reactions, and local injection site reactions), discontinuation for tolerability, number of administrations, number of clinic visits and duration of treatment. These additions were not prespecified and are reported as post hoc outcomes. All effect estimates used in the synthesis,

tables and figures were verified against the full reports and linked companion reports before the final analysis.

Outcomes

The primary outcome was the change in haemoglobin concentration at the end of the treatment period, with 8 to 12 weeks as a prespecified time point. Secondary outcomes were correction of anaemia; repletion of iron stores measured by serum ferritin and transferrin saturation; markers of iron excess; time to haematological response; quality of life; fatigue; adherence; transfusion or retreatment; adverse events by type (hypersensitivity and infusion reactions, local injection site reactions, gastrointestinal intolerance and hypophosphataemia); discontinuation for tolerability; service burden measured by the number of administrations and visits; and change in measured HbA1c after iron repletion. Correction of anaemia and repletion of iron stores were treated as distinct outcomes because haemoglobin can normalise while iron stores remain depleted.

Risk of bias assessment

Risk of bias was assessed with version 2 of the Cochrane risk of bias tool for randomised trials (RoB 2) [27] for the effect of assignment to intervention on the primary haemoglobin outcome, across 5 domains: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. G.K. and A.C.M.N. assessed all 13 included trials by consensus, and M.O. provided methodological adjudication where required. Judgements were made conservatively where methods were incompletely reported. Risk of bias plots were produced with robvis [28].

Data synthesis

Random effects meta-analysis was used only when studies were sufficiently similar in population, comparison, outcome metric and follow up. The exploratory quantitative synthesis compared endpoint haemoglobin concentrations at 12 weeks rather than changes from baseline. Each mean difference was calculated as ferric carboxymaltose minus iron sucrose, with its sampling variance taken as the sum across arms of SD^2/n . Values reported in g/L, including their standard deviations, were divided by 10 to obtain g/dL. Between study variance was estimated by restricted maximum likelihood, pooled effects used inverse variance weights, and 95% confidence intervals used the normal approximation.

Heterogeneity was quantified with Cochran's Q and I^2 . The calculation was reconstructed independently in Python using NumPy and SciPy, and the extracted data are provided in Additional file 2. All other results were synthesised narratively following SWiM [23]. For the narrative synthesis, studies were grouped by comparison into 4 groups: IV against oral iron; IV preparation against IV preparation; IV iron against placebo or standard medical care; and iron with an adjunctive therapy against the same or a comparable iron regimen. Within each group, the direction and size of the effect reported by each study were summarised for each outcome, tabulated with study design, follow up and risk of bias, and interpreted alongside the certainty of the evidence. Planned subgroup analyses were by diabetes status, IV preparation, cumulative dose, country income group and risk of bias. The original 2010 date floor was

retained as a sensitivity analysis. Funnel plots and statistical tests for small study effects were not used, because no comparison included 10 or more trials; the risk of reporting bias was instead considered within the GRADE assessment.

Certainty of the evidence

Certainty was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for each clinically distinct comparison and outcome, rather than for the review as a single body of evidence. Randomised evidence started at high certainty and was downgraded where warranted for risk of bias, inconsistency, indirectness, imprecision and publication bias. G.K., A.C.M.N. and M.O. completed the assessment after data extraction, synthesis and RoB 2 judgements had been finalised.

Use of large language models

In September and October 2026, we used Claude, a large language model developed by Anthropic, as an assistive tool to organise extracted material, support drafting and check consistency between the text, tables and figures. All title and abstract screening and full text assessment took place in EPPI-Reviewer; the model did not screen, include or exclude any record and did not mark any record as ineligible at any stage. The authors made and verified all eligibility decisions, completed data extraction, assessed risk of bias and certainty of the evidence, and determined the conclusions. ChatGPT (OpenAI) was also used for language editing, consistency checks and manuscript organisation. The authors reviewed the final text, verified all scientific claims and retain full responsibility for the work. Neither model meets the criteria for authorship.

Protocol amendments after registration

In total, 5 amendments were introduced after registration and before the final synthesis (Table 2). Applying the registered diabetes criterion would have produced an empty review, because no identified trial recruited on diabetes status or reported outcomes stratified by diabetes. Retaining the route restriction and the 2010 date floor would have excluded both direct IV against oral trials, which were published in 2009. The amended review therefore broadened population and comparator eligibility, moved diabetes status to a prespecified subgroup and applicability question, moved the date floor to 2000, and accepted end of treatment haemoglobin while retaining 8 to 12 weeks as a prespecified time point. The title was updated to describe the evidence actually synthesised. These consequences are taken into account when the results are interpreted.

Table 2
Protocol amendments and rationale

Amendment	As registered	As conducted	Reason
Comparator	IV iron compared with oral iron; eligibility based on route	Any iron therapy compared with any other intervention	Amended during study selection, before the final synthesis. The registered route restriction would have left only 2 direct route comparison trials, both published in 2009
Population	Females with diabetes mellitus and anaemia related to heavy menstrual bleeding	Females with anaemia related to heavy menstrual bleeding, with diabetes status as a prespecified subgroup	Amended during study selection, before the final synthesis. Diabetes as an eligibility requirement would have yielded no included trial, so it was retained as a prespecified subgroup and applicability question
Date floor	Studies published from 2010 onwards	Retrieval restricted to reports published from 2000 onwards in every database; the 2010 floor retained as a sensitivity analysis	Amended during study selection, before the final synthesis. The 2010 floor would have excluded 3 included studies, including both direct route comparison trials and the double blind sham controlled trial
Primary outcome window	Haemoglobin at 8 to 12 weeks	Haemoglobin at the end of the treatment period, with 8 to 12 weeks as 1 prespecified time point	Amended before the final synthesis because follow up ranged from 2 to 12 weeks. The 8 to 12 week window was retained as a prespecified time point and used for pooling where comparable data were available
Title	Intravenous versus Oral Iron Therapy for Heavy Menstrual Bleeding Related Iron Deficiency Anaemia: Evidence and Applicability to Females with Diabetes Mellitus	Iron Therapy for Heavy Menstrual Bleeding Related Iron Deficiency Anaemia: Efficacy, Tolerability and Evidence Gaps for Women with Diabetes Mellitus. A Systematic Review	Updated after the scope amendments so that the title describes the evidence actually synthesised rather than an IV against oral, diabetes specific evidence base that the search did not identify

IV intravenous

Results

Study selection

The search identified 736 records. After removal of 178 duplicates, 558 records were screened by title and abstract, of which 478 were excluded and 80 reports were sought for full text retrieval. Of these, 27 could not be retrieved, leaving 53 reports for full text assessment (Fig. 1). Most unretrieved reports were conference abstracts or grey literature, and several appeared to be preliminary or duplicate accounts of studies later included. Full texts were sought through library services, interlibrary loan and open access repositories. Eligibility could not be confirmed for the unretrieved reports, and missed eligible evidence cannot be ruled out.

Of the 53 reports assessed, 11 were excluded for documented reasons, and the remaining 42 reports corresponded to 13 studies that met the amended eligibility criteria. The 558 screened records corresponded to 520 distinct titles; the other 38 were additional reports of the same studies, such as conference abstracts, trial register entries and secondary publications, which were linked to their parent study at the full text stage and counted once rather than removed as duplicate references. A large part of the retrieved set addressed the management of HMB rather than the prevention or treatment of iron deficiency or IDA, which explains the small proportion of eligible studies.

Characteristics of included studies

Table 3 gives an overview of the included studies and their principal findings, and Table 4A and Table 4B summarise design, population, interventions, outcomes, follow up, safety and interpretation. The studies were conducted in the United States, Mexico, the Republic of Korea, Japan, India and Pakistan. The evidence base was concentrated in high income and Asian settings, and no study was identified from sub Saharan Africa. Study populations included women with IDA specifically related to HMB, and preoperative gynaecological populations in which HMB was one of several underlying causes. Trials recruiting only women whose anaemia resulted from HMB provide direct evidence, whereas trials in mixed preoperative populations provide partial evidence, because an unknown proportion of participants had anaemia from other causes. Results from the latter are reported separately and were downgraded for indirectness in the certainty assessment.

Table 3
Included studies and principal findings

Study	Country	N	Intervention	Comparator	Main finding
Muneyyirci-Delale 2007 [15]	USA	110	Goserelin plus oral ferrous sulfate	Sham plus the same oral ferrous sulfate	Adjunctive goserelin improved Hb; the randomised contrast is goserelin, not iron dose or route
Kim 2009 [9]	Korea	76	IV iron sucrose	Oral iron protein succinylate	Hb rise 3.0 vs 0.8 g/dL; target Hb ≥ 10 g/dL: 76.7% vs 11.5%
Van Wyck 2009 [10]	USA and Mexico	477	IV FCM	Oral ferrous sulfate	Hb rise ≥ 2 g/dL: 82% vs 62%; Hb correction: 73% vs 50%; QoL favoured FCM
Wolf 2013 [16]	USA	69 randomised; 55 treated	IV FCM	IV iron dextran	Similar Hb efficacy; FCM caused transient FGF23 mediated hypophosphataemia; 10 cases < 2.0 mg/dL vs none
Seid 2014 [17]	USA	344 AUB subgroup	IV ferumoxytol	Placebo	Mean Hb rise 2.8 vs 0.0 g/dL; fatigue, vitality and energy improved more with ferumoxytol
Mahey 2016 [11]	India	60 randomised; 58 analysed	IV FCM	IV IS	Faster Hb rise at 6 weeks; no significant Hb difference at 12 weeks; fewer FCM administrations
Seid 2017 [18]	USA, multicentre	789 HMB subgroup	IV FCM	SMC, mostly oral iron	HMB subgroup: highest post randomisation Hb 11.68 vs 10.89 g/dL; ferritin 101.62 vs 20.94 ng/mL
Ikuta 2019 [19]	Japan	238	IV FCM	SFO	FCM noninferior for maximum Hb change and required fewer administrations over a shorter treatment period
Lee 2019 [12]	Korea	101	IV FCM	IV IS	Hb ≥ 10 g/dL by 2 weeks: 78.8% vs 72.3%; time to

Study	Country	N	Intervention	Comparator	Main finding
					threshold 7.7 vs 10.5 days
Tahir 2019 [20]	Pakistan	334 randomised	IV IS	IV IS plus erythropoietin	Day 14 Hb 10.59 ± 1.21 vs 11.93 ± 0.62 g/dL; the combination produced faster correction
Kawabata 2022 [13]	Japan	357	IV FDI	SFO	FDI noninferior for Hb; marked reduction in hypophosphataemia and administration burden
Yagi (Ninjin'yoeito) 2022 [21]	Japan	40 enrolled; 30 analysed	Oral sodium ferrous citrate	The same iron plus NYT	Hb improved similarly ($P = 0.72$); NYT improved fatigue and anxiety. Mixed gynaecological population; HMB applicability limited
Chaturvedi 2024 [14]	India	60	IV FCM	IV IS	At 12 weeks Hb 12.6 ± 0.6 vs 12.7 ± 0.5 g/dL; FCM required fewer doses; 1 participant with diabetes in each arm

AUB abnormal uterine bleeding, FCM ferric carboxymaltose, FDI ferric derisomaltose, FGF23 fibroblast growth factor 23, Hb haemoglobin, HMB heavy menstrual bleeding, IS iron sucrose, IV intravenous, NYT Ninjin'yoeito, QoL quality of life, SFO saccharated ferric oxide, SMC standard medical care

Table 4
A Study design, population, outcomes and follow up

Study	Design	Population	Outcomes	Follow up
Muneyyirci-Delale 2007 [15]	Phase III, multicentre, double blind	Premenopausal women with IDA due to leiomyomas	Hb; bleeding; transfusion; uterine and fibroid volume	12 weeks of treatment plus 24 weeks of follow up
Kim 2009 [9]	Phase IV, open label, randomised	Menorrhagia; Hb < 9 g/dL; preoperative	Hb rise; ferritin; target Hb $\geq$ 10 g/dL; safety	3 weeks
Van Wyck 2009 [10]	Phase III, open label, randomised, 84 sites	IDA plus HMB; Hb $\leq$ 11 g/dL	Hb response and correction; ferritin and TSAT; QoL; AEs	6 weeks
Wolf 2013 [16]	Open label, multicentre, randomised	IDA secondary to HMB	FGF23 and phosphate primary; Hb secondary; AEs	35 days
Seid 2014 [17]	Double blind, randomised, placebo controlled; subgroup analysis	AUB plus IDA; Hb 7 to 10 g/dL; oral iron unsuccessful	Hb; FACIT-F; SF-36 vitality; energy; safety	5 weeks
Mahey 2016 [11]	Randomised controlled, open label	IDA due to AUB or HMB; PBAC > 100	Hb; ferritin; target Hb; QoL; AEs; cost	12 weeks
Seid 2017 [18]	Open label, multicentre, randomised	Postpartum or HMB IDA; HMB stratum analysed separately	Safety primary; Hb and ferritin efficacy	30 days
Ikuta 2019 [19]	Open label, noninferiority, multicentre, randomised	IDA due to hypermenorrhoea; Japanese participants	Maximum Hb change primary; iron indices; safety; visits	About 8 weeks
Lee 2019 [12]	Open label, multicentre, randomised	Menorrhagia plus preoperative IDA	Hb $\geq$ 10 g/dL by 2 weeks; time to Hb threshold; QoL; AEs	2 weeks for efficacy
Tahir 2019 [20]	Randomised clinical trial	IDA awaiting major gynaecological surgery; causes included fibroids, adenomyosis, endometriosis and dysfunctional uterine bleeding	Hb at day 14; safety	14 days

Study	Design	Population	Outcomes	Follow up
Kawabata 2022 [13]	Phase III, open label, active controlled, noninferiority, randomised	IDA associated with menorrhagia; Japanese participants	Maximum Hb change; iron indices; phosphate; AEs; administration burden	Treatment plus 4 weeks of follow up
Yagi (Ninjin'yoito) 2022 [21]	Open label, single centre, phase II, randomised	Preoperative anaemia with mixed gynaecological diseases; a subset had menorrhagia	Hb; fatigue; anxiety; ferritin; safety	At least 10 days preoperatively; mean about 40 days
Chaturvedi 2024 [14]	Prospective, open label, randomised	Perimenopausal HMB; Hb 6 to 10 g/dL; oral iron intolerant or non compliant	Hb; ferritin and iron; doses; AEs	12 weeks

AE adverse event, AUB abnormal uterine bleeding, FACIT-F Functional Assessment of Chronic Illness Therapy Fatigue scale, FGF23 fibroblast growth factor 23, Hb haemoglobin, HMB heavy menstrual bleeding, IDA iron deficiency anaemia, PBAC pictorial blood loss assessment chart, QoL quality of life, SF-36 36 item Short Form Health Survey, TSAT transferrin saturation

Table 4
B Interventions, efficacy, safety and interpretation

Study	Intervention and comparator	Efficacy findings	Safety and tolerability	Interpretation for synthesis
Muneyyirci-Delale 2007 [15]	Both arms ferrous sulfate 325 mg TID; goserelin 10.8 mg vs sham	Hb LS mean difference + 1.17 g/dL favouring goserelin; >2 g/dL response OR 6.36	Adverse events in 89% of participants in both groups, reported as an aggregate frequency; no serious drug related event	Retained as adjunctive cointervention evidence; not pooled as an iron against iron comparison
Kim 2009 [9]	IV IS vs oral iron protein succinylate 80 mg/day	Hb + 3.0 vs + 0.8 g/dL; target achieved 76.7% vs 11.5%	Tolerable AEs in both arms	Direct route comparison; high risk of bias because the efficacy analysis excluded poorly compliant participants
Van Wyck 2009 [10]	FCM up to 1000 mg weekly vs ferrous sulfate 325 mg TID	Hb $\geq$ 2 g/dL: 82% vs 62%; correction to Hb $\geq$ 12 g/dL: 73% vs 50%	No serious drug related AEs	Direct IV against oral evidence; objective laboratory outcomes and > 90% completion
Wolf 2013 [16]	FCM 15 mg/kg (maximum 1000 mg) vs iron dextran at equivalent dose	Hb response was secondary; iron indices improved in both arms	Phosphate < 2.0 mg/dL in 10 FCM vs 0 dextran	Mechanistic safety trial; contributes mainly to the hypophosphataemia findings
Seid 2014 [17]	Ferumoxytol 510 mg $\times$ 2 vs placebo	Hb + 2.8 vs 0.0 g/dL; significantly greater improvement in fatigue, vitality and energy	Safety assessed in the parent trial	Conference abstract and subgroup report; useful but less detailed than full articles
Mahey 2016 [11]	FCM $\leq$ 1000 mg weekly vs IS 300 mg twice weekly	6 weeks Hb 12.30 vs 11.48 g/dL; 12 weeks 12.36 vs 12.10 g/dL	Asymptomatic hypophosphataemia 15 vs 12; resolved	FCM accelerated early correction and reduced visits; efficacy at 12 weeks converged
Seid 2017 [18]	Single FCM 15 mg/kg (maximum 1000 mg) vs investigator selected SMC	HMB: highest Hb 11.68 vs 10.89 g/dL; highest ferritin 101.62 vs 20.94 ng/mL	Serious AEs 0.6% FCM vs 2.2% SMC overall	HMB stratified results are directly relevant; SMC heterogeneous and mostly oral iron

Study	Intervention and comparator	Efficacy findings	Safety and tolerability	Interpretation for synthesis
Ikuta 2019 [19]	FCM vs SFO	Adjusted maximum Hb change difference – 0.15 g/dL (95% CI – 0.35 to 0.04), meeting noninferiority	Phosphate decreases occurred in both arms	Similar Hb efficacy with lower treatment burden for FCM
Lee 2019 [12]	Single dose FCM vs multiple doses of IS	Hb ≥ 10 g/dL: 78.8% vs 72.3%; time 7.7 vs 10.5 days (P = 0.013)	No major between group safety signal reported	FCM mainly improved speed and convenience rather than the response proportion at 2 weeks
Tahir 2019 [20]	IS 200 mg on alternate days vs the same IS plus erythropoietin 5000 IU	Day 14 Hb 10.59 ± 1.21 vs 11.93 ± 0.62 g/dL (P < 0.05)	No adverse effects attributed to erythropoietin reported	Adjunctive erythropoietin trial; the randomised contrast is a cointervention, not the iron formulation
Kawabata 2022 [13]	FDI vs SFO	Hb noninferiority; difference + 0.06 g/dL (95% CI – 0.13 to 0.24)	Phosphate < 2.0 mg/dL: 8.4% vs 83.2%; ≤ 1.0 mg/dL: 0 vs 6.7%	Strongest comparative evidence on preparation specific phosphate risk and service burden
Yagi (Ninjin'yoeto) 2022 [21]	Oral iron 100 mg/day vs the same iron plus NYT 7.5 g/day	Hb 9.9 to 11.9 vs 9.8 to 12.0 g/dL; between group Hb change P = 0.72	One liver dysfunction event in the NYT group	Indirect evidence because only part of the population had HMB; retained as contextual adjunctive evidence, not pooled
Chaturvedi 2024 [14]	FCM vs IS	12 weeks Hb 12.6 ± 0.6 vs 12.7 ± 0.5 g/dL; overall Hb rise 4.97 vs 4.63 g/dL	Minor reactions; no major safety signal	Direct HMB evidence; diabetes reported in 1 participant per arm but no diabetes stratified outcomes

AE adverse event, CI confidence interval, FCM ferric carboxymaltose, FDI ferric derisomaltose, Hb haemoglobin, HMB heavy menstrual bleeding, IS iron sucrose, IU international units, IV intravenous, LS least squares, NYT Ninjin'yoeto, OR odds ratio, SFO saccharated ferric oxide, SMC standard medical care, TID 3 times daily

Comparisons evaluated

Direct comparisons of IV with oral iron came from 2 studies, both published in 2009 (Kim 2009 [9]; Van Wyck 2009 [10]). Later trials mainly compared IV preparations or dosing strategies. A further 3 reports

assessed adjunctive or non iron comparators with iron therapy in 1 or both arms (Muneyyirci-Delale 2007 [15]; Tahir 2019 [20]; Yagi 2022 [21]); these were included under the widened comparator framework but analysed separately, and they are not treated as evidence that 1 iron preparation is superior to another. The comparative evidence therefore falls into 4 clinically distinct groups: IV against oral iron; IV preparation against IV preparation; IV iron against placebo or standard medical care; and iron with an adjunctive therapy against the same or a comparable iron regimen. Data were pooled only when intervention, comparator, outcome metric and follow up were sufficiently similar.

This distribution shows that recent research has concentrated on formulation, dosing and delivery rather than route of administration. It should not be read as evidence that the route question has been settled, because only 2 direct route comparison trials were identified and both are dated.

Risk of bias

In total, 3 trials were judged at high risk of bias for the primary haemoglobin outcome (Kim 2009, Wolf 2013 and Lee 2019), and the remaining 10 had some concerns. No trial was judged at low overall risk of bias (Table 5; Fig. 2 and Fig. 3).

Table 5
Risk of bias for the primary haemoglobin outcome

Study	Randomisation	Deviations	Missing data	Measurement	Reported result	Overall
Muneyyirci-Delale 2007 [15]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Kim 2009 [9]	Low	High	High	Low	Some concerns	High
Van Wyck 2009 [10]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Wolf 2013 [16]	Some concerns	Some concerns	High	Low	Low	High
Seid 2014 [17]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Mahey 2016 [11]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Seid 2017 [18]	Low	Low	Some concerns	Low	Some concerns	Some concerns
Ikuta 2019 [19]	Some concerns	Low	Low	Low	Low	Some concerns
Lee 2019 [12]	Some concerns	Some concerns	High	Low	Some concerns	High
Tahir 2019 [20]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Kawabata 2022 [13]	Some concerns	Low	Low	Low	Low	Some concerns
Yagi (Ninjin'yoito) 2022 [21]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Chaturvedi 2024 [14]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

Judgements follow RoB 2 for the effect of assignment to intervention on the primary haemoglobin outcome. Incompletely reported methods were judged conservatively. G.K. and A.C.M.N. completed the assessments by consensus, with methodological adjudication by M.O. where required

Figure 2 Risk of bias for the primary haemoglobin outcome in each included trial

Judgements were made with RoB 2 for the effect of assignment to intervention and correspond to Table 5.

Figure 3 Distribution of risk of bias judgements across the 13 included trials

Unweighted percentages of study level judgements for the primary haemoglobin outcome in each RoB 2 domain and overall, as reported in Table 5.

Haemoglobin response

Quantitative synthesis was possible for haemoglobin at 12 weeks in 2 trials directly comparing ferric carboxymaltose with iron sucrose (Mahey 2016 [11]; Chaturvedi 2024 [14]). Other comparisons were not pooled because of clinically important differences in comparator, follow up, outcome definition or population, and were synthesised narratively.

In the 2 direct comparisons of IV and oral iron, IV iron produced a larger and faster haematological response. Kim 2009 [9] reported a mean haemoglobin rise of 3.0 against 0.8 g/dL, with target haemoglobin reached in 76.7% against 11.5% of participants. Van Wyck 2009 [10] reported a haemoglobin increase of at least 2.0 g/dL in 82% against 62% and correction to at least 12 g/dL in 73% against 50%. Because response definitions and treatment schedules differed, these trials were not pooled.

Compared with placebo, ferumoxytol increased mean haemoglobin by 2.8 against 0.0 g/dL through week 5 in the subgroup analysis by Seid 2014 [17], and this rise was accompanied by greater improvements in fatigue, vitality and energy. In the HMB stratum of Seid 2017 [18], ferric carboxymaltose achieved higher post randomisation haemoglobin and ferritin values than heterogeneous standard medical care, which consisted mostly of oral iron.

Direct comparisons between IV formulations consistently showed similar final haemoglobin correction, with differences in speed of response, treatment burden and safety. Ikuta 2019 [19] and Kawabata 2022 [13] met their prespecified noninferiority criteria for haemoglobin. Lee 2019 [12] found similar proportions reaching haemoglobin of at least 10 g/dL within 2 weeks (78.8% against 72.3%), with a shorter estimated time to that threshold for ferric carboxymaltose (7.7 against 10.5 days). Mahey 2016 [11] found higher haemoglobin with ferric carboxymaltose at 6 weeks, but values converged by 12 weeks. In the exploratory random effects meta-analysis of Mahey 2016 [11] and Chaturvedi 2024 [14], which together included 118 analysed participants, the pooled mean difference in haemoglobin at 12 weeks was - 0.00 g/dL (95% confidence interval - 0.32 to 0.31; I^2 23%) (Fig. 4). This estimate showed no detectable difference between the preparations. Because only 2 small trials contributed, both the pooled effect and the estimate of heterogeneity should be interpreted with caution.

Figure 4 Haemoglobin at 12 weeks, ferric carboxymaltose against iron sucrose

Exploratory random effects meta-analysis of endpoint haemoglobin, calculated as ferric carboxymaltose minus iron sucrose, using restricted maximum likelihood and normal approximation confidence intervals. A mean difference above 0 favours ferric carboxymaltose. In total, 2 trials with 118 analysed participants contributed. Pooled mean difference - 0.00 g/dL (95% confidence interval - 0.32 to 0.31); I^2 23%. Because only 2 small trials contributed, both the pooled estimate and the estimate of heterogeneity are imprecise,

and the result does not establish equivalence. CI confidence interval, FCM ferric carboxymaltose, IS iron sucrose, MD mean difference, REML restricted maximum likelihood, SD standard deviation.

Overall pattern of the evidence

Where the 2 routes were compared directly, IV iron corrected anaemia faster than oral iron. Head to head trials of IV formulations generally showed comparable final haemoglobin responses, and the differences between them lay mainly in time to response, number of administrations and phosphate related safety. The adjunctive trials indicate that suppressing menstrual blood loss with goserelin or stimulating erythropoiesis with erythropoietin can accelerate haemoglobin recovery when combined with iron, but these effects cannot be attributed to the iron regimen itself. Trials that enrolled women awaiting gynaecological surgery for a range of conditions, only some of whom had HMB, are less directly relevant to the review question and are reported separately.

Tolerability and hypophosphataemia

Serum phosphate was reported in 4 of the 13 trials [11, 13, 16, 19], and the clearest differences between preparations were in serum phosphorus rather than haemoglobin. Kawabata 2022 [13] found serum phosphorus below 2.0 mg/dL in 8.4% of participants given ferric derisomaltose against 83.2% of those given saccharated ferric oxide. Severe hypophosphataemia, defined as serum phosphorus of 1.0 mg/dL or less, occurred in 6.7% of the saccharated ferric oxide group and in none of the ferric derisomaltose group. Ikuta 2019 [19] observed decreased blood phosphorus in about 1 in 5 participants in both arms, with the lowest group mean values near 1.45 mg/dL. Wolf 2013 [16] reported intact and C terminal fibroblast growth factor 23 (FGF23) alongside serum phosphate in women with heavy uterine bleeding, providing a mechanistic explanation that is reviewed in detail elsewhere [5, 6]. In Mahey 2016 [11], asymptomatic hypophosphataemia occurred in 15 participants given ferric carboxymaltose and 12 given iron sucrose, with recovery within 6 to 12 weeks.

Hypophosphataemia and treatment delivery burden were not prespecified in the registered protocol and are therefore post hoc outcomes. These findings are exploratory and require confirmation in prospectively specified comparisons.

Reporting of adverse events varied substantially. Reported events included gastrointestinal intolerance, hypersensitivity or infusion reactions, local administration site reactions and treatment discontinuation, but definitions and reporting practices were too inconsistent for quantitative comparison by event type, so study specific data are presented. Kawabata 2022 [13] reported treatment emergent adverse events in 66.2% of participants given ferric derisomaltose and 90.8% of those given saccharated ferric oxide, including urticaria, pyrexia and rash, with treatment interruption and withdrawal but no serious treatment related events. Muneyyirci-Delale 2007 [15] reported adverse events in 89% of participants in both arms, with no serious drug related events. Yagi 2022 [21] recorded 1 episode of liver dysfunction in the adjunctive arm. Van Wyck 2009 [10] and Kim 2009 [9] reported no serious drug related events. This heterogeneity in reporting is a limitation of the evidence base.

Service burden

In total, 4 studies quantified the number of administrations needed to deliver an equivalent total iron dose. Kawabata 2022 [13] reported a mean of 1.65 administrations for ferric derisomaltose against 9.72 for saccharated ferric oxide, and 92.8% against 43.2% of participants received the full cumulative dose within the treatment period; the shortfall was attributed to treatment interruption for hypophosphataemia rather than insufficient treatment time. Ikuta 2019 [19] found a mean of 2.7 against 12.0 administrations, with mean treatment durations of 15.4 days for ferric carboxymaltose and 39.3 days for saccharated ferric oxide. Lee 2019 [12] reported a single visit for ferric carboxymaltose against 3 to 8 visits for iron sucrose. Mahey 2016 [11] reported a mean of 1.8 doses of ferric carboxymaltose against 4.7 doses of iron sucrose ($P < 0.001$). Chaturvedi 2024 [14] also reported that ferric carboxymaltose required fewer doses than iron sucrose.

Quality of life and fatigue

Patient reported outcomes were assessed in a minority of studies. Van Wyck 2009 [10] reported that quality of life favoured ferric carboxymaltose over oral iron. Seid 2014 [17] showed greater improvement with ferumoxytol than with placebo in fatigue measured by the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F), in vitality measured by the 36 item Short Form Health Survey (SF-36) and in linear analogue energy scores. Lee 2019 [12] found no significant difference in quality of life between ferric carboxymaltose and iron sucrose, despite faster correction and fewer visits with ferric carboxymaltose. Yagi 2022 [21] reported similar haemoglobin improvement with iron alone and with iron plus Ninjin'yoeito, whereas fatigue and anxiety improved more with the adjunctive herbal treatment; because this population was mixed, the finding is indirect evidence for IDA related to HMB.

Diabetes mellitus

No study recruited participants on the basis of diabetes, and no trial reported treatment effects stratified by diabetes status or change in HbA1c after iron repletion. Chaturvedi 2024 [14] reported 1 participant with diabetes mellitus in each treatment arm (3.33% of each group). This reflects how diabetes was reported rather than showing that women with diabetes were absent from the trials. The available evidence therefore cannot show whether iron efficacy, hypophosphataemia risk, tolerability or service burden differ in women with diabetes, and applicability to this population remains a substantial evidence gap.

Subgroup and sensitivity analyses

None of the planned subgroup analyses could be performed, because no more than 2 trials contributed to any pooled comparison and no trial reported results by diabetes status. Applying the original 2010 date floor would have removed 3 included studies (Muneyyirci-Delale 2007 [15], Kim 2009 [9] and Van Wyck 2009 [10]) and with them all direct IV against oral evidence; it would not have changed the pooled estimate, which rests on trials published in 2016 and 2024. Reporting bias could not be assessed statistically for the same reason that subgroup analyses were not possible.

Studies excluded at full text

Of the 11 reports excluded after full text assessment, 2 had the wrong population, 6 were not randomised comparative trials, 1 did not report extractable data for an eligible subgroup, 1 was not a primary comparative study and 1 did not evaluate iron therapy. The excluded reports and reasons are listed in Table 6.

Table 6
Full text exclusions and reasons

Report	Reason for exclusion
Klein et al. 2009 [29]	Intervention is not iron therapy. This record was retrieved through a digital object identifier adjacent to that of an included study
Onken et al. 2014, REPAIR-IDA trial [30]	Wrong population: chronic kidney disease
Berber et al. 2014 [31]	Eligible subgroup data not extractable. About 2 in 3 participants had hypermenorrhoea, but the underlying cause was treated before iron therapy began and no outcome is reported by aetiology
ClinicalTrials.gov NCT01067547, 2009 [32]	Wrong population: inflammatory bowel disease
ClinicalTrials.gov NCT04915196, 2021 [33]	Not a comparative trial: telephone survey of gastrointestinal tolerability
Salimath et al. 2024 [34]	Not a randomised trial: retrospective propensity matched cohort of 14894 women with menorrhagia comparing ferric carboxymaltose with iron sucrose, reporting transfusion avoidance and emergency attendance
Garrone et al. 2017 [35]	Single arm, no comparator: retrospective evaluation of 41 women
Auerbach et al. 2009 [36]	Single arm, no comparator
Auerbach et al. 2011 [37]	Single arm, no comparator
Burn-Murdoch et al. 2017 [38]	Observational, not a comparative trial: service review in which 10 of 84 patients had menorrhagia
Bregman and Goodnough 2014 [3]	Not a primary comparative study: narrative review

Certainty of the evidence

Certainty ratings by comparison and outcome are presented in Table 7. Certainty was low for IV against oral iron and for the pooled ferric carboxymaltose against iron sucrose comparison, and moderate for

haemoglobin across IV preparations, for hypophosphataemia with ferric derisomaltose against saccharated ferric oxide and for the number of administrations. Where no eligible comparative outcome data existed, as for diabetes and HbA1c, certainty was not estimable.

Table 7
Certainty of evidence by comparison and outcome

Comparison and outcome	Evidence base	Certainty	Reason for rating	Interpretation
IV vs oral iron: haemoglobin	Kim 2009 [9]; Van Wyck 2009 [10]	Low	Downgraded for risk of bias and imprecision: only 2 direct route comparison trials, both published in 2009, with differing outcome definitions and treatment schedules	IV iron produced faster haematological correction in the available direct comparisons, but the evidence does not support a universal route preference
IV preparation vs IV preparation: haemoglobin	Mahey 2016 [11]; Ikuta 2019 [19]; Lee 2019 [12]; Kawabata 2022 [13]; Chaturvedi 2024 [14]	Moderate	Downgraded for risk of bias. Haemoglobin is an objective outcome and findings were broadly consistent, but most trials were open label and several incompletely reported allocation concealment or analysis procedures	Final haemoglobin responses were broadly similar across the preparations studied; this does not establish that all IV iron products are interchangeable
FCM vs IS: haemoglobin at 12 weeks	Mahey 2016 [11]; Chaturvedi 2024 [14]; 118 analysed participants; pooled MD – 0.00 g/dL (95% CI – 0.32 to 0.31), I ² 23%	Low	Downgraded for risk of bias and serious imprecision: only 2 small trials contributed and the confidence interval is compatible with differences in either direction	Exploratory pooled estimate; it does not establish equivalence or noninferiority
FDI vs SFO: hypophosphataemia	Kawabata 2022 [13]	Moderate	Large directly measured difference between groups, downgraded because the evidence comes from a single open label trial	Formulation specific evidence; further comparative confirmation is warranted
IV preparations: administrations and treatment visits	Ikuta 2019 [19]; Mahey 2016 [11]; Lee 2019 [12]; Kawabata 2022 [13]	Moderate	Objective treatment delivery outcome with a consistent direction across 4 head to head trials; downgraded because the evidence base is	Higher dose preparations generally required fewer administrations; this is not evidence of cost effectiveness

Comparison and outcome	Evidence base	Certainty	Reason for rating	Interpretation
			limited and regimen specific	
Diabetes status and HbA1c	No eligible diabetes stratified treatment effect or HbA1c outcome data	Not estimable	No comparative outcome data were available. Chaturvedi 2024 [14] reported 1 participant with diabetes in each arm but no diabetes stratified outcomes	Diabetes specific comparative effectiveness and HbA1c effects remain an evidence gap

CI confidence interval, FCM ferric carboxymaltose, FDI ferric derisomaltose, HbA1c glycated haemoglobin, IS iron sucrose, IV intravenous, MD mean difference, SFO saccharated ferric oxide. Certainty was rated with the Grading of Recommendations Assessment, Development and Evaluation approach

Discussion

Principal findings

This systematic review shows that the comparative evidence for iron therapy in women with IDA related to HMB is clinically relevant but uneven. The trials differ in the preparations compared, the comparator, the length of follow up and the outcomes reported, so few answer the same question in the same way and most comparisons rest on 1 or 2 trials. The review has 4 principal findings.

First, direct comparative evidence between IV and oral iron is limited and dated. The 2 route comparison trials were published in 2009 [9, 10], and later research has concentrated on comparisons among IV formulations. Recent trials have therefore asked which IV preparation restores iron most efficiently, safely and conveniently, rather than whether IV iron is superior to oral iron. The absence of recent route comparisons leaves uncertainty about how contemporary oral regimens compare with IV treatment in this population, and the findings do not establish a universal route preference.

Second, the available head to head trials indicate broadly comparable haemoglobin restoration across the IV preparations studied [11, 12, 13, 14, 19]. In the exploratory meta-analysis of ferric carboxymaltose (FCM) against iron sucrose at 12 weeks, the pooled mean difference was essentially null (MD – 0.00 g/dL, 95% CI – 0.32 to 0.31; I² 23%). Only 2 trials could be combined, and they met the pooling rule because they compared the same 2 preparations at the same time point in comparable populations. Their pooled estimate was centred close to zero, but the confidence interval remained compatible with differences of about 0.3 g/dL in either direction, so the analysis does not demonstrate equivalence or noninferiority. With only 2 studies, the estimate of heterogeneity is itself imprecise, and the result is best regarded as an exploratory summary rather than a definitive comparative estimate. It concerns haemoglobin alone and says nothing about whether iron stores were equally replete at the same time point, which is the outcome

that governs recurrence in women who continue to bleed. The findings suggest that, when an adequate dose is delivered, differences between preparations are more evident in the speed and convenience of administration and in preparation specific adverse effects than in final haemoglobin concentration; they do not establish equivalence among all IV iron products.

Third, treatment burden emerged as a key differentiator among IV formulations. Several newer preparations allow larger doses per visit and therefore need substantially fewer treatment encounters than iron sucrose or saccharated ferric oxide [11, 12, 13, 14, 19]. This matters for women with HMB, who may need repeated treatment during ongoing investigation or management of blood loss. Fewer infusions may reduce travel, time away from work or caregiving, use of infusion facilities and opportunities to discontinue treatment, which is especially relevant where infusion capacity is limited. However, the included studies rarely measured these outcomes directly as patient reported or health service measures, so the findings describe differences in treatment delivery rather than evidence of cost effectiveness.

Fourth, the safety profiles of IV preparations are not interchangeable. Hypophosphataemia was notable in studies of FCM and other IV formulations [11, 13, 16, 19], and Wolf et al. linked hypophosphataemia after FCM to changes in FGF23 and renal phosphate handling [16]. Evidence from populations other than HMB also shows clinically important differences in hypophosphataemia between IV formulations and indicates that repeated exposure, higher cumulative doses and preexisting risk factors need careful consideration [4, 5, 6, 39]. Expert consensus supports risk assessment and serum phosphate monitoring in patients at increased risk or receiving repeated high dose FCM [39], which is particularly relevant in HMB, where recurrent iron loss may require several treatment courses over the years.

Interpretation in the context of existing evidence

This pattern is consistent with the wider IV iron literature: when adequate replacement doses are given, haematological efficacy alone may not distinguish contemporary preparations. The choice of formulation should therefore take account of the total iron deficit, the maximum dose per administration, the number of visits, the speed of correction, any history of intolerance, the adverse effect profile, local availability and cost.

The distinction between the rate of response and the final haemoglobin response is clinically important. Several included studies showed earlier haemoglobin improvement or earlier attainment of targets with higher dose IV preparations [11, 12], and where later follow up was available, no meaningful difference remained [11, 14]. For clinically stable women, this convergence suggests that convenience, tolerability and cost may matter more than a small early difference. Rapid correction may be essential before surgery, in severe symptomatic anaemia, when oral treatment has failed or is not tolerated, or when ongoing menstrual loss makes slow replacement inadequate. The evidence supports individualised treatment selection rather than a universal hierarchy of preparations.

The adjunctive trials need separate consideration. Muneyyirci-Delale et al. [15] compared goserelin with sham in women who all received oral ferrous sulfate, Tahir et al. [20] assessed the addition of

erythropoietin to IV iron, and Yagi et al. [21] evaluated Ninjin'yoeito alongside iron therapy. These trials describe approaches that may speed recovery or improve symptoms but do not compare iron formulations or routes, and they should not be interpreted or pooled as such comparisons.

Diabetes, HbA1c and applicability

The most consequential evidence gap concerns diabetes mellitus. No included trial was designed for women with diabetes, and diabetes stratified treatment effects were unavailable. One trial reported 1 participant with diabetes in each arm [14], far too few for a subgroup analysis. The absence of diabetes specific evidence should therefore not be read as evidence that women with diabetes were absent from the trials; rather, diabetes was largely invisible in the reporting.

This omission matters because iron status can influence the interpretation of HbA1c. A systematic review of anaemia and erythrocyte abnormalities found that iron deficiency, with or without anaemia, was generally associated with higher HbA1c without a corresponding increase in glucose indices [7]. A 2023 systematic review and meta-analysis of 10 studies and 2113 participants found that HbA1c decreased after iron replacement in 9 of the 10 studies [8], and earlier studies in people with diabetes showed reductions in HbA1c after iron replacement despite little or no change in measured glucose [40, 41].

The literature is not fully consistent, however. Meta-analyses have reported substantial heterogeneity and uncertainty about the size and direction of the effect, particularly in people with diabetes [8, 42]. These data do not justify a numerical correction of HbA1c in women with IDA, but they do support a clinically relevant conclusion: iron status should be considered when HbA1c is interpreted around the time of IDA diagnosis or treatment, particularly when HbA1c lies close to a diagnostic or therapeutic threshold.

For women with both diabetes and IDA related to HMB, this creates an important intersection between menstrual health, haematology and diabetes care. Correction of iron deficiency could change HbA1c independently of true glycaemic improvement, while recurrent menstrual blood loss may repeatedly alter iron status. Future trials should record diabetes at baseline, report glucose lowering therapy and glycaemic status, and measure HbA1c alongside direct measures of iron repletion. Where erythrocyte turnover or iron deficiency may compromise HbA1c, alternative or complementary measures of glycaemia should be considered.

Safety and hypophosphataemia

Hypophosphataemia illustrates why haemoglobin efficacy should not be the only basis for choosing an IV iron preparation. In the included trials, serum phosphate fell after several IV preparations, but the magnitude and frequency varied [11, 13, 16, 19]. Mechanistic evidence implicates increased biologically active FGF23, leading to renal phosphate wasting, reduced calcitriol and secondary disturbance of mineral metabolism [5, 6, 16].

For most patients receiving a single course, biochemical hypophosphataemia may be transient and asymptomatic. Concern increases with repeated exposure, persistent hypophosphataemia or additional

risk factors. Recent expert consensus therefore recommends phosphate monitoring for patients at increased risk or requiring repeated high dose courses rather than universal testing of every low risk recipient of FCM [39]. This distinction is relevant in HMB, where recurrent blood loss can lead to repeated treatment. Trials in this population should report serum phosphate systematically, specify its timing and severity, and follow participants long enough to distinguish transient biochemical change from persistent clinically relevant effects.

Patient reported outcomes and service burden

Correction of haemoglobin is an important treatment goal, but it does not capture the full burden of IDA related to HMB. Fatigue, impaired physical functioning, reduced work capacity and diminished quality of life are clinically meaningful consequences of iron deficiency, yet only a minority of the included studies assessed patient reported outcomes [10, 12, 17, 21], with differing instruments and follow up periods.

Future comparative trials should therefore complement laboratory outcomes with validated measures of fatigue, health related quality of life, menstrual symptoms and functional recovery, and should measure treatment burden explicitly. The number of infusions is a useful process indicator, but patient time, travel, missed work, caregiving responsibilities, infusion chair use and health system costs would show more completely whether the convenience of high dose preparations translates into meaningful benefit for patients and services.

Geographical representation and health equity

The geographical distribution of the evidence limits its generalisability. No included trial was conducted in sub Saharan Africa, despite the substantial burden of anaemia and menstrual health problems in the region. Feasibility depends on context, and access to laboratory testing, IV formulations, infusion facilities and specialist gynaecological services varies widely between health systems.

Evidence generated mainly in higher resource settings may underestimate implementation constraints where infusion services are scarce. Conversely, preparations that need fewer visits could offer substantial advantages in such settings if procurement costs, safety monitoring and supply chains are manageable. Comparative effectiveness studies in low and middle income settings should therefore evaluate feasibility, affordability, acceptability and health system resource requirements as well as haemoglobin correction.

Strengths and limitations

A strength of this review is its focus on a clinically coherent but under synthesised problem: iron replacement in women whose IDA is associated with HMB. The review separates direct iron comparisons from adjunctive interventions, examines outcomes beyond haemoglobin, including hypophosphataemia and treatment delivery burden, and explicitly evaluates applicability to women with diabetes. Protocol

amendments are reported with their timing, rationale and consequences, and multiple reports were linked to their parent studies so that studies rather than publications formed the unit of inclusion.

Several limitations should temper interpretation. First, eligibility criteria were broadened after registration in response to an unexpectedly sparse evidence base. Although the amendments were made before the final synthesis and are reported transparently, post registration changes can introduce bias at review level, and the results are therefore interpreted alongside the consequences of the original criteria. Second, full texts could not be retrieved for 27 of the 80 reports sought. Most were conference abstracts and supplement items with no full report, but an eligible trial could lie among them. Third, the evidence base is heterogeneous in formulation, dosing, comparator, severity of anaemia, definition of HMB, follow up and outcome reporting; most comparisons rest on 1 or 2 trials, most trials were open label, and the meta-analysis of FCM against iron sucrose provides limited precision. Some studies addressed preoperative correction of anaemia, which may not reflect long term management of recurrent HMB. Fourth, hypophosphataemia and treatment delivery burden were added after the review began and are exploratory outcomes, and patient reported outcomes and longer term safety were inconsistently reported. Fifth, concomitant treatment of menstrual blood loss, including hormonal and antifibrinolytic therapy, was not consistently reported, which limits assessment of its influence on haematological outcomes; this should not be read as evidence that such treatment was absent. Finally, diabetes specific conclusions are limited mainly by non reporting: the diabetes findings identify an evidence gap rather than demonstrating equivalent treatment effects in women with and without diabetes.

Implications for practice

For women with IDA related to HMB who need IV iron, the evidence does not support choosing among IV preparations on the basis of final haemoglobin response alone. Treatment selection should take account of the urgency and size of the iron deficit, the number of infusions, tolerability, preparation specific safety, previous response, patient preference, service capacity and cost. Higher dose preparations may reduce the number of visits, but this convenience should be weighed against formulation specific risks, particularly hypophosphataemia in susceptible patients or those needing repeated treatment.

The trials comparing IV with oral iron are too few and too old to support a universal route preference. This does not apply to tolerability: the poor gastrointestinal tolerance of oral iron, and the poor adherence that follows from it, rest on a separate body of evidence [2] that has not been superseded. Oral iron remains appropriate where it is tolerated, effective and fast enough for the clinical situation, whereas IV iron may be particularly useful where rapid correction is needed, oral therapy is ineffective or poorly tolerated, adherence is problematic, or ongoing blood loss makes oral replacement inadequate.

Implications for multidisciplinary care

The findings support including questions about menstrual blood loss, fatigue and treatment tolerance in the clinical assessment of women receiving care for anaemia. Gynaecologists, general practitioners, midwives and nurses can explain the prescribed treatment schedule, assess barriers to adherence and

attendance, and document symptoms and laboratory follow up. When IV iron is prescribed, adverse event surveillance and phosphate monitoring should follow the preparation specific protocol and the assessed risk of the patient [13, 16, 39]. Communication with gynaecology and diabetes teams is relevant when ongoing bleeding or iron repletion complicates the interpretation of HbA1c [7, 8]. These are clinical implications of the treatment evidence; the included trials did not establish the effectiveness of any specific care pathway.

Implications for research

Future trials should move beyond showing that different iron preparations raise haemoglobin. Priorities include adequately powered contemporary comparisons of oral and IV treatment; standardised definitions of HMB and IDA; common time points for haemoglobin, ferritin and transferrin saturation; systematic phosphate monitoring where relevant; validated patient reported outcomes; and formal measurement of treatment and health service burden. Treatment directed at the bleeding itself, including hormonal management and tranexamic acid, should be recorded at baseline and during follow up, because it alters continuing blood loss and therefore the response attributed to iron.

Diabetes should be incorporated prospectively rather than treated as an unreported comorbidity. Trials should record diabetes type, duration, treatment and baseline glycaemic status, and report treatment effects by diabetes status where sample size permits. Studies designed for women with coexisting HMB, IDA and diabetes are warranted, particularly to determine whether iron repletion changes HbA1c independently of glycaemia and whether this affects clinical decisions. Greater geographical representation is also needed: trials in sub Saharan Africa and other resource constrained settings should evaluate effectiveness together with feasibility, acceptability, affordability and service capacity, to establish whether the lower administration burden of newer IV preparations translates into meaningful advantages where access to infusion services is limited.

Conclusions

Comparative evidence for iron therapy in IDA related to HMB has shifted from direct comparisons of IV and oral treatment to comparisons among IV preparations. The available trials suggest broadly similar eventual haemoglobin responses among the IV preparations studied, while clinically important differences may lie in speed of correction, number of administrations and preparation specific adverse effects, particularly hypophosphataemia.

The evidence does not establish that all IV preparations are interchangeable, nor does it provide a contemporary answer to the IV against oral question. Women with diabetes remain inadequately represented in the reporting of this literature, despite evidence that iron deficiency and its correction can influence HbA1c independently of glycaemia. Future research should integrate menstrual, haematological and metabolic outcomes and evaluate effectiveness, safety, patient experience and service burden across a broader range of health systems, with multidisciplinary teams of gynaecologists, midwives, nurses and diabetes specialists central to assessment, education and follow up.

Abbreviations

AE

adverse event

AUB

abnormal uterine bleeding

CENTRAL

Cochrane Central Register of Controlled Trials

CI

confidence interval

CINAHL

Cumulative Index to Nursing and Allied Health Literature

FACIT-F

Functional Assessment of Chronic Illness Therapy Fatigue scale

FCM

ferric carboxymaltose

FDI

ferric derisomaltose

FGF23

fibroblast growth factor 23

GRADE

Grading of Recommendations Assessment, Development and Evaluation

Hb

haemoglobin

HbA1c

glycated haemoglobin

HMB

heavy menstrual bleeding

IDA

iron deficiency anaemia

IS

iron sucrose

IU

international units

IV

intravenous

LS

least squares

MD

mean difference

NYT

Ninjin'yoeito
OR
odds ratio
PBAC
pictorial blood loss assessment chart
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO
International Prospective Register of Systematic Reviews
QoL
quality of life
RoB 2
version 2 of the Cochrane risk of bias tool for randomised trials
SD
standard deviation
SF-36
36 item Short Form Health Survey
SFO
saccharated ferric oxide
SMC
standard medical care
SWiM
Synthesis Without Meta-analysis
TID
3 times daily
TSAT
transferrin saturation

Declarations

Ethics approval and consent to participate

Not applicable. This review used published data and involved no human participants, human tissue or identifiable human data.

Consent for publication

Not applicable.

Availability of data and materials

Study level findings, risk of bias judgements, certainty ratings and full text exclusions are included in this published article, the full search strategies are included as Additional file 1, and the dataset supporting the exploratory 12 week meta-analysis is included as Additional file 2.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

G.K. conceived and coordinated the review, formulated the review question, developed and registered the protocol with PROSPERO, and designed the eligibility criteria and data extraction framework. G.K. and A.A.K. independently screened titles and abstracts and assessed full text reports for eligibility. G.K. completed the data extraction. G.K. and A.C.M.N. completed the RoB 2 assessments by consensus, with M.O. providing methodological adjudication where required. G.K., A.C.M.N. and M.O. completed the GRADE assessment. G.K. synthesised the data, prepared the tables and figures, and drafted the manuscript. G.K. is the corresponding author and guarantor of the review.

A.A.K. served as information specialist and second reviewer. She designed, peer reviewed and executed the search strategies, managed deduplication and the reference library, independently screened records and assessed full text reports with G.K., and contributed to reporting the search process.

M.O. and G.K. contributed to the methodological development of the review, including refinement of the review question, eligibility criteria, synthesis plan and certainty assessment, provided methodological adjudication for RoB 2, contributed to the GRADE assessment and the interpretation of the findings, and critically revised the manuscript.

F.N. provided senior supervision and oversight of the review, contributed to its conceptual and methodological development, supported the interpretation of the findings from a global health perspective, and critically revised the manuscript for important intellectual content.

F.K. and M.S. resolved screening disagreements as third reviewers, contributed clinical and contextual expertise to the interpretation of the findings across health care settings, and critically revised the manuscript.

E.R. and J.H.S. provided clinical expertise in obstetrics and gynaecology and contributed to the clinical framing, outcome selection and interpretation of the findings.

S.R. provided expertise in nutritional epidemiology and iron status, contributed to the outcome definitions and the interpretation of the iron related findings, and critically reviewed the manuscript.

U.L. contributed expertise in menstrual health and research methodology, including the interpretation of menstrual health outcomes, and critically revised the manuscript.

L.K. and B.P.K. contributed clinical and contextual expertise in diabetes care and women's health and critically reviewed the manuscript.

D.N. contributed clinical and contextual expertise to the interpretation of the findings and critically reviewed the manuscript.

A.C.M.N. took part in the risk of bias and certainty assessments with G.K. and M.O., contributed to the interpretation of the findings, and critically revised the manuscript.

C.S. contributed public health and contextual expertise, particularly on the applicability of the findings in African health care settings, and critically reviewed the manuscript.

E.S. provided expertise in diabetes and endocrinology, particularly on the findings related to diabetes, iron status and HbA1c, and critically revised the manuscript.

S.B. contributed data management and data science expertise to the organisation of the review records and data and critically reviewed the manuscript.

N.C., B.M., S.N.L. and K.K. contributed clinical, epidemiological and contextual expertise on the relevance of the findings to health care settings in Tanzania and other resource constrained settings and critically reviewed the manuscript.

E.K. contributed expertise in nursing, public health and the East African health care context, supported the interpretation of the findings, and critically reviewed the manuscript.

C.W. provided senior scientific and methodological oversight, contributed to the design of the review, guided the statistical and evidence synthesis methods, supported the interpretation of the findings, and critically revised the manuscript for important intellectual content.

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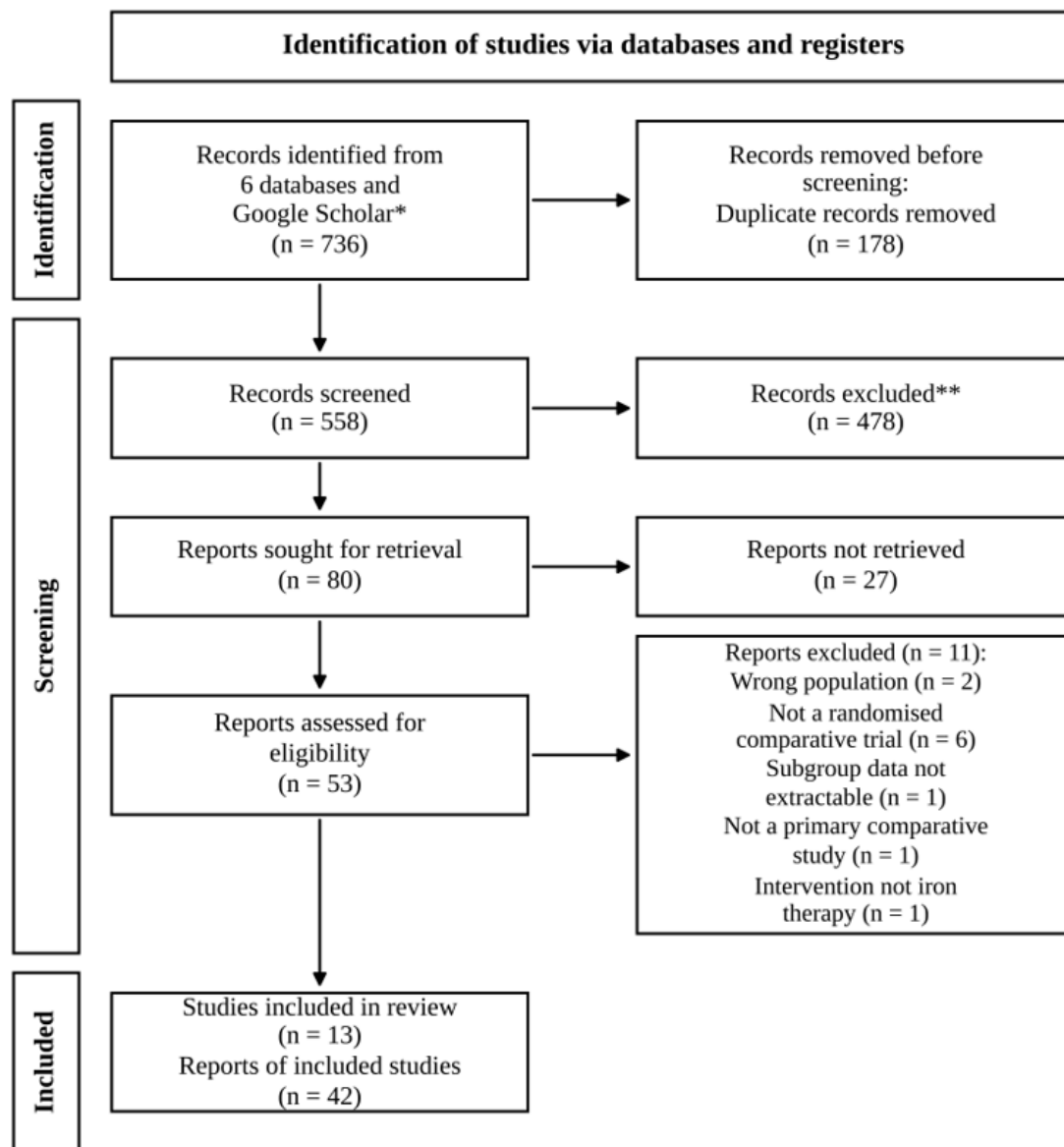
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Figures



*MEDLINE, Embase, CENTRAL, CINAHL, Scopus, Web of Science and Google Scholar; trial registries and reference lists were also searched.

**All records were screened by 2 independent reviewers; no automation tools were used to exclude records.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

Figure 1

PRISMA 2020 flow diagram of study selection

Records were identified from 6 bibliographic databases and Google Scholar. Reasons for exclusion at full text: wrong population (n = 2), not a randomised comparative trial (n = 6), eligible subgroup data not extractable (n = 1), not a primary comparative study (n = 1) and intervention not iron therapy (n = 1). Layout adapted from the PRISMA 2020 flow diagram for databases and registers [22].

	D1	D2	D3	D4	D5	Overall
Muneyyirci-Delale 2007	?	+	?	+	?	?
Kim 2009	+	-	-	+	?	-
Van Wyck 2009	?	?	+	+	?	?
Wolf 2013	?	?	-	+	+	-
Seid 2014	?	+	?	+	?	?
Mahey 2016	?	?	+	+	?	?
Seid 2017	+	+	?	+	?	?
Ikuta 2019	?	+	+	+	+	?
Lee 2019	?	?	-	+	?	-
Tahir 2019	?	?	?	+	?	?
Kawabata 2022	?	+	+	+	+	?
Yagi (Ninjin'yoito) 2022	?	?	+	+	?	?
Chaturvedi 2024	?	?	+	+	?	?

D1 Randomisation process D2 Deviations from intended interventions
D3 Missing outcome data D4 Measurement of the outcome
D5 Selection of the reported result

Judgement
+ Low
? Some concerns
- High

Figure 2

Risk of bias for the primary haemoglobin outcome in each included trial

Judgements were made with RoB 2 for the effect of assignment to intervention and correspond to Table 5.

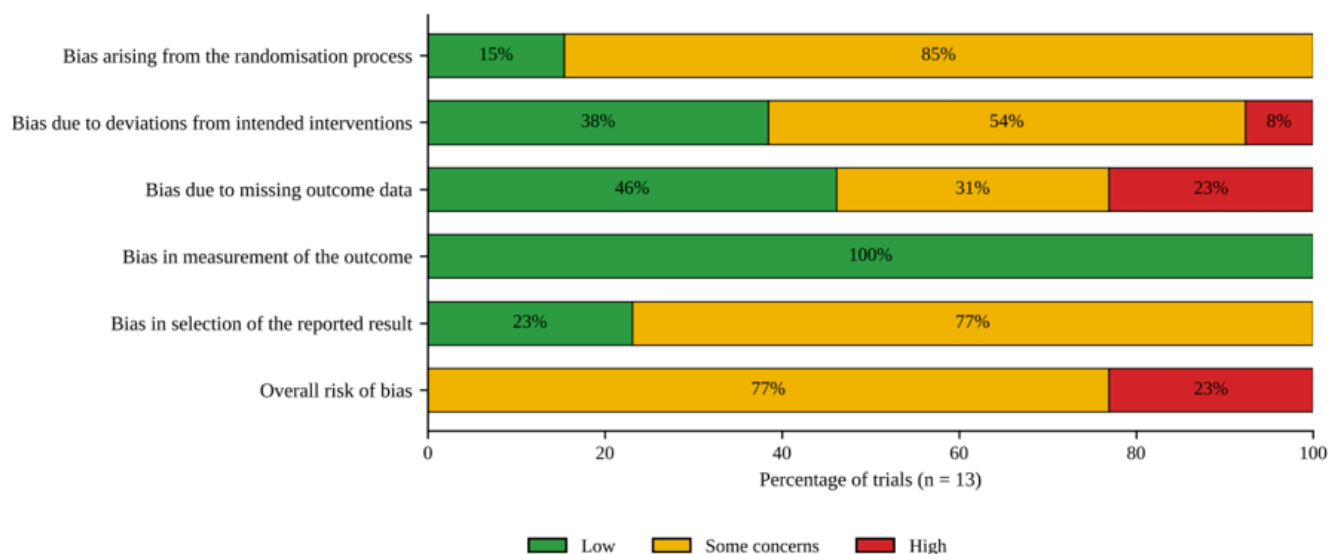


Figure 3

Distribution of risk of bias judgements across the 13 included trials

Unweighted percentages of study level judgements for the primary haemoglobin outcome in each RoB 2 domain and overall, as reported in Table 5.

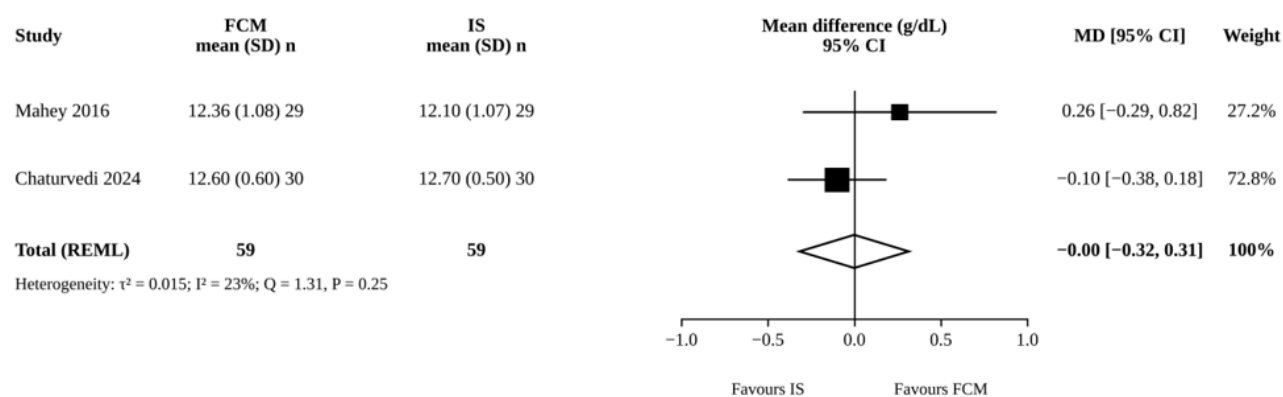


Figure 4

Haemoglobin at 12 weeks, ferric carboxymaltose against iron sucrose

Exploratory random effects meta-analysis of endpoint haemoglobin, calculated as ferric carboxymaltose minus iron sucrose, using restricted maximum likelihood and normal approximation confidence intervals. A mean difference above 0 favours ferric carboxymaltose. In total, 2 trials with 118 analysed participants contributed. Pooled mean difference -0.00 g/dL (95% confidence interval -0.32 to 0.31); I^2 23%. Because only 2 small trials contributed, both the pooled estimate and the estimate of heterogeneity are imprecise,

and the result does not establish equivalence. CI confidence interval, FCM ferric carboxymaltose, IS iron sucrose, MD mean difference, REML restricted maximum likelihood, SD standard deviation.

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