Iron (Fe) preparations for women of Reproductive age with Iron Deficiency Anaemia in pregnancy: FRIDA, a systematic review and network meta-analysis

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Abstract

Background

Numerous iron preparations are available for the treatment of iron deficiency anaemia in pregnancy. We aimed to provide a summary of the effectiveness and safety of iron preparations used in this setting.

Methods

We did a systematic review and network meta-analysis of randomised trials. We searched Medline, Embase, Cochrane Central Register of Controlled Trials, trial registers and grey literature for trials published in any language from Jan 1, 2011 to Feb 28, 2021. We included trials of pregnant women with IDA evaluating iron preparations, irrespective of administration route with ≥ 60 mg of elemental iron, in comparison to another iron or non-iron preparation. Three independent reviewers selected studies, extracted data, and did a risk of bias assessment using the Cochrane tool (version 1·0). The outcomes were haemoglobin (primary) in g/L and serum ferritin in mcg/L (secondary) levels at four weeks from baseline and treatment-related severe and non-severe adverse events. We did random-effects pairwise and network meta-analyses. The effect measure is reported as mean difference (MD) with 95% confidence intervals (CI). Side-effects were reported descriptively for each trial. This study is registered with PROSPERO, number CRD42018100822.

Findings

Among 3037 records screened, 128 full-text articles were further assessed for eligibility. Of the 53 eligible trials (reporting on 9145 women), 30 (15 interventions; 3243 women) contributed data to the network meta-analysis for haemoglobin and 15 (nine interventions; 1396 women) for serum ferritin. The risk of bias varied across the trials contributing to network meta-analysis. Compared with oral ferrous sulfate, intravenous iron sucrose improved both haemoglobin (MD 7·17 g/L, 95%CI 2·62-11·73) and serum ferritin (49·66 mcg/L, 13·63-85·69), and intravenous ferric carboxymaltose (8·52 g/L, 0·51-16·53) improved haemoglobin levels. The evidence for other interventions compared with ferrous sulfate was insufficient. The most common side-effects with oral iron preparations were gastrointestinal effects (nausea, vomiting, and altered bowel movements). Side-effects were less common with parenteral iron preparations, although these included local pain, skin irratation, and, on rare occasions, allergic reactions.

Interpretation

Iron preparations for treatment of iron deficiency anaemia in pregnancy vary in effectiveness, with good evidence of benefit for intravenous iron sucrose and some evidence for intravenous ferric carboxymaltose. Clinicians and policy makers should consider the effectiveness of individual preparations before administration, to ensure effective treatment.

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Research in context

Evidence before this study

Iron deficiency anaemia is common in pregnancy due to increasing iron demand and is associated with adverse maternal and perinatal outcomes. Numerous iron preparations are available for treatment, but until now these have only been compared in traditional pairwise meta-analyses, the most comprehensive of which are two Cochrane reviews, published in 2011 and 2015. Before this study (in Feb, 2018, we searched Medline, Embase, The Cochrane Library, and the PROSPERO database for completed or ongoing systematic reviews and network meta-analyses of iron treatments for anaemia in pregnancy. We found no published network meta-analyses or available protocols.

Added value of this study

To our knowledge, our network meta-analysis of randomised trials is the first to simultaneously compare all the widely available iron treatments for anaemia in pregnancy against one another. This work updates existing meta-analyses assessing the effectiveness of iron interventions in pregnant women.

Implications of all the available evidence

Treating iron deficiency anaemia in pregnancy remains a priority. Intravenous iron preparations, including iron sucrose and ferric carboxymaltose, are the most effective at improving haemoglobin and iron stores. Our findings suggest that existing policy on the treatment of anaemia in pregnancy could be updated to reflect that some iron preparations are more effective than others for treating anaemia in pregnancy.

Introduction

Iron deficiency anaemia, the commonest global nutritional deficiency, disproportionately affects women of reproductive age. [1] The burden is particularly severe in pregnancy, affecting half of all pregnant women, due to increased demands, and with many women entering pregnancy with depleted iron stores. A quarter of all mothers are diagnosed with the condition every year even in high-income countries like the UK. [2] Anaemia in pregnancy further predisposes women to maternal mortality [3] and morbidity, including increased haemorrhage, infection, [4] and adverse perinatal outcomes including low birth weight and preterm delivery. [5]

Anaemia is characterised by a fall in haemoglobin, resulting from a progressive deficiency of micronutrients including iron. [6,7] Theoretically, treating iron deficiency anaemia should be straightforward: replace the lost iron. Despite the widespread availability of iron preparations, anaemia in pregnancy remains a problem.[4] There are many widely tested as well as new emerging oral and parenteral forms of iron.[8] But there is no comprehensive comparison of the effectiveness of individual iron preparations. Consequently, clinicians tend to prescribe the most readily available oral iron preparation, which may not be the most effective.

Our aim was to synthesise the available data and provide a summary of effectiveness and safety of iron preparations used for the treatment of iron deficiency anaemia in pregnancy.

Methods

Search strategy and selection criteria

Our systematic review with network meta-analysis was guided by a prospectively developed and protocol (Appendix pp 1-11). The study was registered with PROSPERO (CRD42018100822) and reported in accordance with the PRISMA extension for network meta-analysis. [9]

We included randomised and quasi-randomised controlled trials (RCTs) published in any language assessing the effectiveness of iron preparation in pregnant women with confirmed iron deficiency

anaemia, as defined by trial authors, based on objective testing. Included trials compared one or more iron preparations, with another iron preparation, placebo, no treatment, vitamin (mainly folic acid) and/or mineral supplement (zinc). The iron in the intervention arm was required to contain at least 60 mg of elemental iron, considered the minimum effective dose for treating anaemia. [10,11] We excluded trials comparing two doses of the same iron preparation and those with study groups treated with erythropoietin or blood transfusion, micronutrient or multivitamin supplements, vitamin A, or outdated iron preparations (Appendix p 12). We had originally planned to evaluate the effect of iron preparations in three separate populations: menstruating women, pregnant women and postpartum. In this Article, we present the findings for the pregnant population only, as due to feasibility issues we decided to separate the populations.

Our work builds on two previous Cochrane reviews of iron treatments in pregnant women.[11,12] (Appendix p 12). Thus the literature search was run from 1st January 2011 to 19th July 2018 using a modified search strategy; updated to 28th February 2021 (Appendix p 15). A search, without any language limits, was performed in the major medical literature databases (Appendix p 12). Additionally, we checked the Inside Conferences, Systems for Information in Grey Literature database for grey literature, clinical trial registers for ongoing trials (Appendix pp 12-13) and supplemented this with a random search for relevant trials using Google Scholar. In the first stage, two reviewers (MN, CAP) independently evaluated all retrieved citations, and subsequently the full texts against eligibility criteria. In case of any disagreement, the third reviewer (JD) was consulted.

We collected study-level data using a bespoke data extraction form piloted on five eligible trials. [13-17] We collected information on women's characteristics, evaluated interventions and routinely collected data about trials (Appendix p 13). The trials were then classified by income group based on the World Bank classification, [18] into low, and lower-middle income counties (LMIC) and upper middle and high-income as high-income countries (HIC). For outcome data reported in various units, we extracted values (and their variances) of haemoglobin and serum ferritin as reported by the authors and converted to g/L and mcg/L respectively; we kept a record of conversions. We also recorded details of blood samples

collection (point of care or laboratory tests). Three researchers (MN, CAP and JD) extracted all available data on included trials independently. We did not contact the study authors for any additional information. Publications written in Spanish were translated by CAP, any other non-English publications were translated using Google translate.

The quality of all included trials was assessed using the Cochrane risk of bias tool (version 1·0) classifying trials for each domain, except blinding of outcome assessor, as low, unclear or high risk of bias. [19] We assumed the potential risk of detection bias caused by the lack of blinding of the outcome assessor would be negligible as our main outcome of interest is a laboratory blood test, which is objectively measured.

The assessments of individual domains were then used to obtain a global risk of bias (low, medium or high) for trials contributing to the main network meta-analysis of haemoglobin. We also assessed indirectness of the study groups in accordance with the recommendation of the GRADE working group.[20] The distribution of evidence quality, defined as global risk of bias, is graphically presented for the network analysis of haemoglobin as in Confidence in Network Meta-Analysis approach. [21,22]

We determined effectiveness of iron preparations by changes in haemoglobin (the primary outcome) and serum ferritin (secondary outcome). The effect measure for both outcomes is the mean difference (MD) reported with the respective 95% confidence intervals (CIs). We did not undertake quantitative synthesis of side effects, we reported these descriptively for each trial.

The network meta-analysis for haemoglobin comprised of studies comparing individual iron preparations meeting our inclusion criteria. We assumed that all interventions were jointly randomisable and the concomitant interventions (vitamins and/or minerals) did not have a substantial impact on the outcomes. If any included trials comprised study arms of iron preparations with and without concomitant interventions, we combined the data into one arm using recommended methods. [19] The

arms containing placebo, no intervention, or vitamins and/or minerals were grouped together and coded as 'non-iron intervention'.

We anticipated challenges due to variation in treatment duration, the time between the iron intervention administration, and measurement of laboratory outcomes in the included trials. [11,12,23] To address this we consulted an independent panel of experts (obstetric haematologists, midwives and senior obstetricians) from the British Society for Haematology. We held a consultation meeting prior to embarking on the analyses (on 28th November 2018) during which approaches to grouping iron preparations, strategies for analyses and data presentation were discussed. Following this consultation, we decided to record the timing of haemoglobin measurement from baseline in all trials and analyse the change in the blood parameters at the most commonly reported time point. The network map was generated for both efficacy outcomes and examined for its connectivity (presence of closed loops).[22]

Data analysis

Firstly, extracted data were inspected in a pairwise meta-analysis where more than two trials for the same comparison were available using a random effects model with the restricted maximum likelihood estimator to account for heterogneity if present. [24,25] We quantified inconsistencies between studies in the pairwise meta-analyses using the I^2 statistic [26]. The network meta-analysis assumed consistency using a frequentist approach with a 'contrast-based' model. [22] We assumed constant heterogeneity variance across all comparisons, and estimated the between-study heterogeneity using τ. The within-study correlation because of multi-arm trials was managed using a multivariate random-effects network meta-analysis using the *network* suite of commands in Stata version 15·1 (StataCorp. Texas, USA). [27] Inconsistency between direct and indirect sources of evidence was examined locally using a node-splitting approach, [22,28,29] and globally using a design-by-treatment interaction model. [30]

The ranking of treatments for haemoglobin is presented in a tabulated format ordered according to the mean rank value using the surface under the cumulative ranking (SUCRA) curve. [31] Given the complexity of multiple interventions and comparisons, we used iron ferrous sulfate, the current

standard treatment, as the reference arm when presenting and interpreting the data in the analyses for haemoglobin and serum ferritin.

We applied two secondary approaches to grouping of the iron preparations. First, by route of administration (oral, IV, IM) and second by type of iron salt (ferric IM [Fe3+], ferric IV [Fe3+] and ferrous [Fe2+] oral preparations). Lactoferrin, iron amino acid chelate, and arms with 'no iron preparation' (such as placebo, vitamins or no intervention) were kept as separate groups throughout. We pre-specified two sensitivity analyses, in the first we explored the impact of interventions administered alongside iron. In the second, we assessed the impact of trial quality by excluding trials classified as 'at high risk of bias'. Our protocol intended a sensitivity analysis by year of study publication which proved unfeasible (Appendix p 10). Finally, we performed a prespecified subgroup analysis by country income classification.

Role of the funding source

There was no funding source for this study.

Results

Among 3037 records screened, 128 full-text articles were further assessed for eligibility and 53 trials reporting on 9145 women were included (Figure 1). The main reasons for exclusion were non-RCT design (n=26), irrelevant comparison (dose comparison trials, n=16) and irrelevant study population (non-anaemic pregnant women, n=12) (Figure 1). Not all studies contributed to network meta-analysis due to differences in timing of outcome measurement.[32-62] Additionally, there were issues with data credibility in two studies [unpublished; Mol BW, Bordewijk EM, Rogozinska E et al.] which we chose to exclude from the analyses.

The 53 included trials were conducted in 22 different countries between 1969 and 2020, with the majority published after 2000 (n=43). Pregnant women participating in the trials were recruited between the second and third trimester. The baseline haemoglobin level ranged from 60 to 110 g/L with most

women having moderate anaemia (67/109 trial arms with haemoglobin ranging from 70 g/L to 99 g/L). The baseline body weight ranged from 45·9 to 61·8 kg in the trials of parenteral (IV and IM) iron. Information on pre-existing health conditions (e.g. haemoglobinopathies) alongside any co-administered treatment (e.g. malaria infection prophylaxis or treatment) can be found in Appendix (pp 16-22). We included trials that evaluated 19 interventions. The total daily dose of elemental iron across the trials of oral preparations ranged from 60mg[53] to 240mg[14] with majority of dosages being between 100-200mg (Appendix pp 23-29).

Of all included trials, 30 (62 arms; 3243 women) reported on haemoglobin at four weeks from baseline and were included in the network meta-analysis for haemoglobin.[14,17,34,39,50,51,53,61-82] Characteristics of studies contributing and not contributing data to the network meta-analysis are presented in Table 1. These 30 trials compared 15 different interventions – nine oral iron preparations, three IV preparations, a single IM preparation, lactoferrin and a single 'non-iron intervention' (Figure 2A). Six comparisons were evaluated in more than one study and the other comparisons were evaluated in a single trial. IV iron sucrose vs ferrous sulphate were the most frequently compared pair of interventions (seven trials, 695 women), followed by one lactoferrin vs ferrous sulphate (four trials, 457 women), and ferrous fumarate vs IV iron sucrose (four trials, 305 women) (Figure 2A, Appendix p 30).

The risk of bias varied across the trials contributing to the network meta-analysis for haemoglobin, with more than two thirds of studies (22 of 30) judged to have a high or medium global risk of bias (appendix pp 32–33). Random sequence generation was correctly implemented in half of the trials (15 [50%] of 30). Allocation concealment frequently could not be assessed due to insufficient information (23 [77%] of 30), although blinding of staff and participants was assessed as low risk of bias in 15 (50%) of the 30 included trials. Incomplete outcome data were deemed at low risk in 21 (70%) of 30 trials and selective reporting of outcomes was assessed as low risk in 22 (73%) trials. The indirectness of the study population in the included trials was assessed as medium risk in three (10%) of 30 trials. An overview of the network for haemoglobin by the global risk of bias of the trials informing the results

can be found in the appendix (p 32). Trials not included in the network meta-analysis were more often assessed as being at high risk of bias (appendix pp 32–33).

Compared to ferrous sulphate, both IV ferric carboxymaltose (MD 8·52 g/L, 95%CI 0·51-16·53) and IV iron sucrose (MD 7·17 g/L, 95%CI 2·62-11·73) improved haemoglobin levels (Figure 3A). We did not find evidence of an improvement in haemoglobin concentrations between the other interventions and iron ferrous sulfate. There was no evidence to suggest global or local inconsistencies (appendix p 35). The direct and network effects (indirect and direct evidence) were consistent for the majority of comparisons. Interventions with the highest SUCRA values were oral iron ferrous asparto glycinate (85%), intravenous ferric carboxymaltose (81%), and intravenous iron sucrose (78%). Non-iron interventions had the lowest SUCRA value (22%; appendix p 37). The detailed ranking measures, including SUCRA and mean rank, are presented in the appendix (pp 34–38).

Additional analyses based on broad grouping of iron preparations (by route of administration and type of iron salt) found intravenous preparations compared best against no intervention (Appendix pp 39–42). In a subgroup analysis by income category, the evidence on different results based on trials from low-middle income countries were similar to those presented in the analysis for haemoglobin (Appendix pp 50–51). Network meta-analysis based on trials from high income countries was not performed due to the small number of studies in this subgroup (appendix p 52). In the sensitivity analyses limited to trials categorised as low and medium risk of bias, the evidence on IV iron sucrose vs ferrous sulphate was robust (MD 8·29g/L, 95%CI 3·47-13·12) while the evidence on IV ferric carboxymaltose vs ferrous sulphate became imprecise (8·35g/L, 95%CI -0·91-17·61, Appendix pp 46–49). Our estimate of between-study heterogeneity remained consistent with that estimated in the network analysis for haemoglobin and sensitivity analyses for this network (appendix pp 43–49).

Fifteen trials (30 arms; 1,396 women) reported on serum ferritin at four weeks from baseline and were included in the network meta-analysis for serum ferritin.[13,17,53,62,64,66-69,73,76-80]

The network comprises nine interventions – five oral iron preparations, a single IV and a single IM iron preparation, iron amino acid chelate and lactoferrin. The most frequent comparisons were IV iron sucrose vs ferrous sulphate (four trials, 400 women), IV iron sucrose vs ferrous fumarate (three trials, 216 women) and IV iron sucrose vs ferrous ascorbate (two trials, 400 women) and the other comparisons were evaluated in single trials (Figure 2B).

Compared to ferrous sulphate, IV iron sucrose increased serum ferritin levels (MD 49·66 mcg/L, 95%CI 13·63-85·69) (Figure 3B). There was insufficient evidence of increase of serum ferritin levels between the other interventions vs ferrous sulphate, including IV ferric carboxymaltose vs ferrous sulphate (MD 49·46 mcg/L, 95%CI -34·54-133·45) (Figure 3B). There was no evidence to suggest global (chi-squared = 0·38, p-value = 0·54) or local inconsistencies (Appendix p 36). Interventions with the highest SUCRA were IV iron sucrose (82%) and IV ferric carboxymaltose (74%, appendix 38). The detailed ranking measures, including SUCRA and mean rank, are presented in the appendix (pp 34-38).

Safety reporting in trials of iron interventions in pregnancy were highly variable, with many instances of poor reporting, therefore an analysis by individual preparation proved unfeasible. Overall, gastrointestinal side effects (nausea, vomiting and altered bowel movements) were most common with oral iron preparations. There were no appreciable differences between iron preparations. Allergic reactions, including anaphylaxis, although rare, were more commonly reported with intravenous iron preparations. Other reported side effects to parenteral preparations included injection site pain and inflammation, altered taste and hypotension. A comprehensive summary of all side effects as reported and defined in individual trials can be found in the appendix (pp 53-61).

Discussion

Based on our network meta-analysis of 30 RCTs comparing 15 iron preparations in 3,243 women, IV ferric carboxymaltose and IV iron sucrose were the most effective interventions in improving haemoglobin levels four weeks after starting treatment. The findings on iron ferrous asparto glycinate should be interpreted with caution due to the single small trial with high risk of bias contributing to the

evidence. From our network meta-analysis of 15 RCTs comparing nine iron preparations in 1,396 women, IV iron sucrose was the most effective intervention for improving serum ferritin. The evidence from our network meta-analysis for haemoglobin and serum ferritin show the highest certainty for iron sucrose at improving blood values following administration. There were no appreciable differences in rates of side effects between iron preparations.

This is, to our knowledge, the first network meta-analysis to comprehensively assess the effectiveness of many widely available iron treatments for the management of anaemia in pregnancy. We included trials where iron was administered for treating anaemia following a confirmed diagnosis of iron deficiency anaemia based on objective testing,

Our work was guided by a prospectively developed protocol including input from an independent expert clinical panel before analyses were conducted. The panel, comprising senior clinicians and UK policy makers provided advice on the relevance of the iron preparations, the appropriateness of the time points used for the primary and secondary endpoints and on the pre-planned subgroup analyses.

The searches used to identify trials built on two existing Cochrane reviews,[11,12] using several search terms without any limitations, our searches were updated in February 2021, including the most up to date published data. There are several ongoing studies which we were unable to include in the analyses (Appendix pp 62-63).

The included iron interventions were given at variable doses. This reflects real-life clinical practice where no recommended dosing schedules exist, and treatment is largely based on tolerance and response to treatment. Similarly, there was marked variation in the timing of haemoglobin and serum ferritin measurement from commencement of the intervention (e.g. weekly measurements vs just before delivery). We addressed this methodological challenge by using trials evaluating the response to iron interventions four-weeks from commencement. This allowed the largest number of trials to be included, while reducing spurious results from repeated measurements of outcomes. Furthermore, with oral iron

treatment and assuming optimal compliance, a rise in haemoglobin level of 10 g/L every two weeks can be expected. [83] Thus, measuring haemoglobin at four weeks from treatment commencement should provide sufficient time to identify some treatment effect.

The pair-wise meta- analysis found statistical heterogeneity, but our explorations did not reveal any obvious sources of between-study differences in treatment effect. Factors such as different dosing regimens, variation in measurement of haemoglobin and iron levels and differences baseline characteristics between women may all play a role. Finally, the evidence contributing to the networks for haemoglobin and serum ferritin were sparse. Most comparisons in the network were single head to head trials, affecting the overall stability. [84]

Our work summarises the landscape of clinical trials for the treatment of anaemia caused by iron deficiency in a global pregnant population. Our work allows comparisons across and between individual preparations, giving a more comprehensive overview than the existing pairwise meta-analyses presented in the Cochrane reviews. Our work also incorporates studies published since 2011, [11,12] including newer iron and cofactor preparations. Although iron gluconate and iron isomaltoside are often widely used in clinical practice, these preparations were not included in the trials identified in the systematic review, despite contacting authors for additional non published data.

Existing policy on iron preparations for the treatment of anaemia in pregnancy is highly variable. [83,85] The reasons for this are multifactorial including the numerous causes of iron deficiency that exist globally, differences in antenatal care delivery between regions, and sheer number of small trials testing different preparations of iron where outcomes are measured at different time points [23]. [86] We have addressed some of these challenges in our work, but definitive research, including large scale trials measuring clinically relevant endpoints which have long been called for are needed. [87]

The finding from this systematic review show that parenteral iron preparations are more effective at increasing haemoglobin levels compared to oral preparations. This is likely due to improved compliance

with parenteral preparations, improved bioavailability and targeted dosing. [1,88] These findings support other existing meta-analyses of iron interventions.[87,89,90] The clinical impact of higher haemoglobin and iron stores such as improvements in clinical outcomes such as maternal and infant wellbeing remain unknown. [91,92] This further emphasizes the need for good quality trials addressing these questions. [92,93]

Ferrous sulphate is one of the most widely used oral iron preparations, being cheap and widely available, hence we used this as our reference iron preparations. [85] However, published data suggest that tolerance to ferrous fumerate or alternative dosing schedules such as alternate day may improve adherence.[94] The findings from this systematic review show most oral iron preparations perform similarly, however parenteral preparations fair better. Therefore, policy makers and clinicians to consider which oral iron preparation they are using as first line treatment for anaemic women in pregnancy based on availability, and tolerance for each induvial woman rather than what is most widely used.

Our work suggests insufficient evidence to support lactoferrin, a non-iron based cofactor, as beneficial at improving haemoglobin levels or iron stores in pregnant women. Therefore, further clinical trials, especially in diverse settings, are required before firm conclusions can be made. There are two large ongoing trials of lactoferrin use in pregnancy, which once complete are likely to improve the precision of estimates reported in our work (Appendix p 62-63).

We hope our work improves the available evidence and provide some much-needed clarity on which preparations are the most effective, best tolerated and safest for treating anaemia in pregnancy. Future work, building on this review, could include novel trial methodology testing the top-ranking interventions against each other, increasing the available direct evidence. We hope that these data aid policy makers to reconsider the use of less effective iron preparations when treating anaemia in pregnancy.

Word count: 3495 (exc abstract)

Details of Contributions

JD, ER and ST contributed to the study conception and design and planned the statistical analyses. JD, MN and CA collected data, undertook quality assessment. ER and PJG accessed and verified the data. ER, PJG, JZ and CMS analysed the data. JD and ER wrote the first draft of the manuscript and are responsible for the decision to submit the manuscript. RW, PJG, SR, KSK and ST critically revised the manuscript for important intellectual content. All authors commented on the drafts and approved the final draft. JD and ST are the guarantors.

Ethical approval: none required.

Data sharing

The data collected for this systematic review and network meta-analysis can be shared on request, with investigator support and approval thorough a signed data access agreement. This includes aggregate study level data collected, cleaned with a data dictionary and the statistical analysis plan. This will be made available with publication. No additional data are available.

Transparency Declaration

JD affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained.

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Declarations of Interest

JD was a member of an advisory panel assessing the side effect profiles of intravenous iron preparations for Pharmacosmos in 2018. ER and PJG were supported by the UK Medical Research Council (MC_UU_12023/24).

All other co-authors have no declarations of interest.

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Table 1. Characteristics of studies contributing and not contributing data to the main network meta-analysis

Characteristic	Contributed data to the main NMA	Did not contribute data to the main NMA
Number of studies	**30**	**23**
Total number of women*	3,243	4,854
Publication year (median, min-max)	2014 (1969, 2020)	2005 (1978, 2020)
Country income group n (%)		
Low and middle-income countries	22 (73)	14 (61)
Upper-middle and high income countries	8 (27)	9 (39)
Total number of arms	62	47**
Anaemia status at baseline* **		
Mild (109-100 g/L)	11	15
Moderate (99-70 g/L)	44	23
Severe (69-40 g/L)	5	3
Not reported	2	6
Number of unique interventions	15	13
Total number of unique comparisons	19	15
Comparisons		
ferrous asparto glycinate vs ferrous ascorbate	1	
Carbonyl iron vs ferrous fumarate	1	
iron polymaltose complex vs ferrous fumarate		1
Iron chondroitinsulfuric acid complex vs ferrous sulphate	1	
Iron amino acid chelate vs ferrous sulphate	1	
ferrous gluconate vs ferrous sulphate	1	
iron polymaltose complex vs ferrous sulphate	1	
NaFeEDTA vs ferrous sulphate		1
lactoferrin vs ferrous sulphate	4	1
ferrous sulphate vs "no-iron intervention"	1	8
IFB vs "no-iron intervention"		1
ferrous gluconate vs "no-iron intervention"	1	
NaFeEDTA vs "no-iron intervention"		1
IV iron dextran vs "no-iron intervention"	1	
ferrous sulphate vs ferrous sulphate and IV Iron polymaltose complex		1
ferrous sulphate vs IV iron sucrose	7	3
ferrous fumarate vs IV iron sucrose	4	
ferrous ascorbate vs IV iron sucrose	2	
iron polymaltose complex vs IV iron sucrose		1
ferrous sulphate vs IV iron dextran	1	
ferrous gluconate vs IV iron dextran	1	
ferrous fumarate vs IV iron dextran		1
lactoferrin vs IV iron dextran		1
ferrous fumarate vs IV iron polymaltose complex		1
ferrous sulphate vs IV ferric carboxymaltose	1	
IV iron sucrose vs IV ferric carboxymaltose	2	
IV iron sucrose vs IV iron dextran	1	2
ferrous sulphate vs IM iron dextran		2
ferrous sulphate vs IM iron sorbitol citric acid		1
IV iron sucrose vs IM iron sorbitol citric acid	3	

NMA, network meta-analysis; IV, intravenous; IM, intramuscular
**The number of women analysed in eligible arms*
***Arms in two originally 3-arm studies with iron and iron and vitamins vs placebo (Sun 2010, Ma 2010) were combined into one*
****Values correspond to number of arms not studies*

Figures

Figure 1. Study selection flow

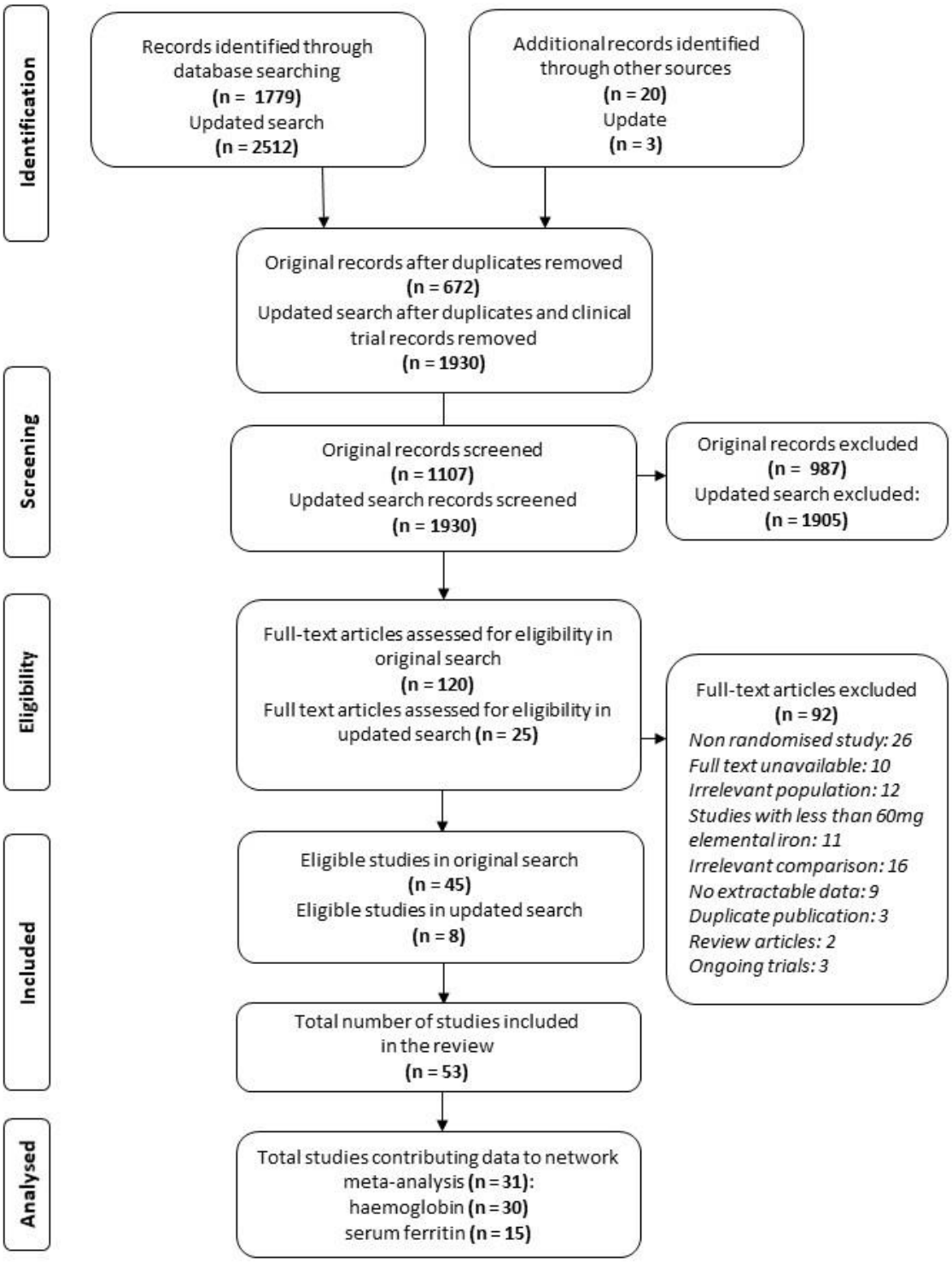


Figure 2. Network map for haemoglobin level and serum ferritin measured around four weeks from baseline

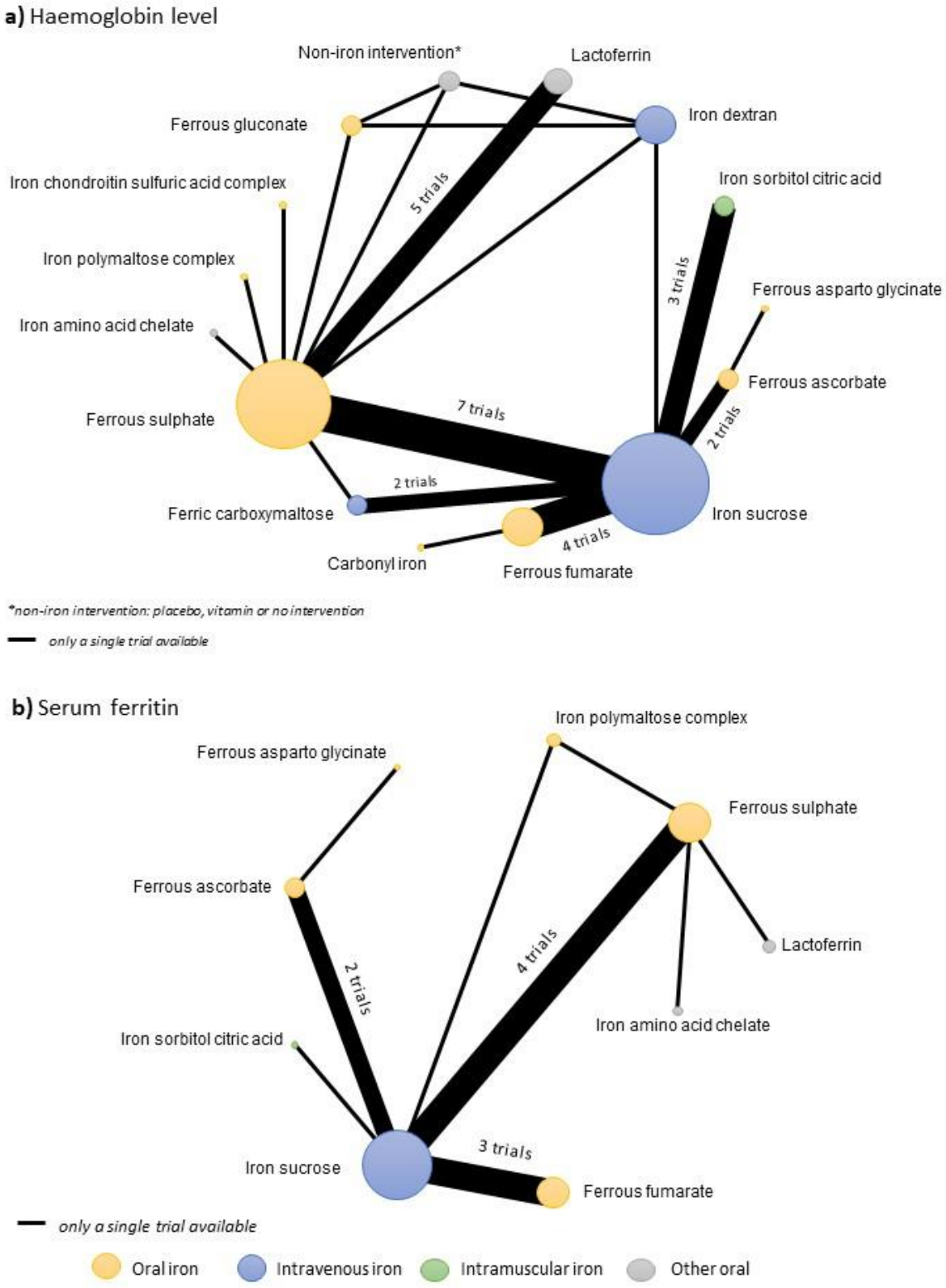
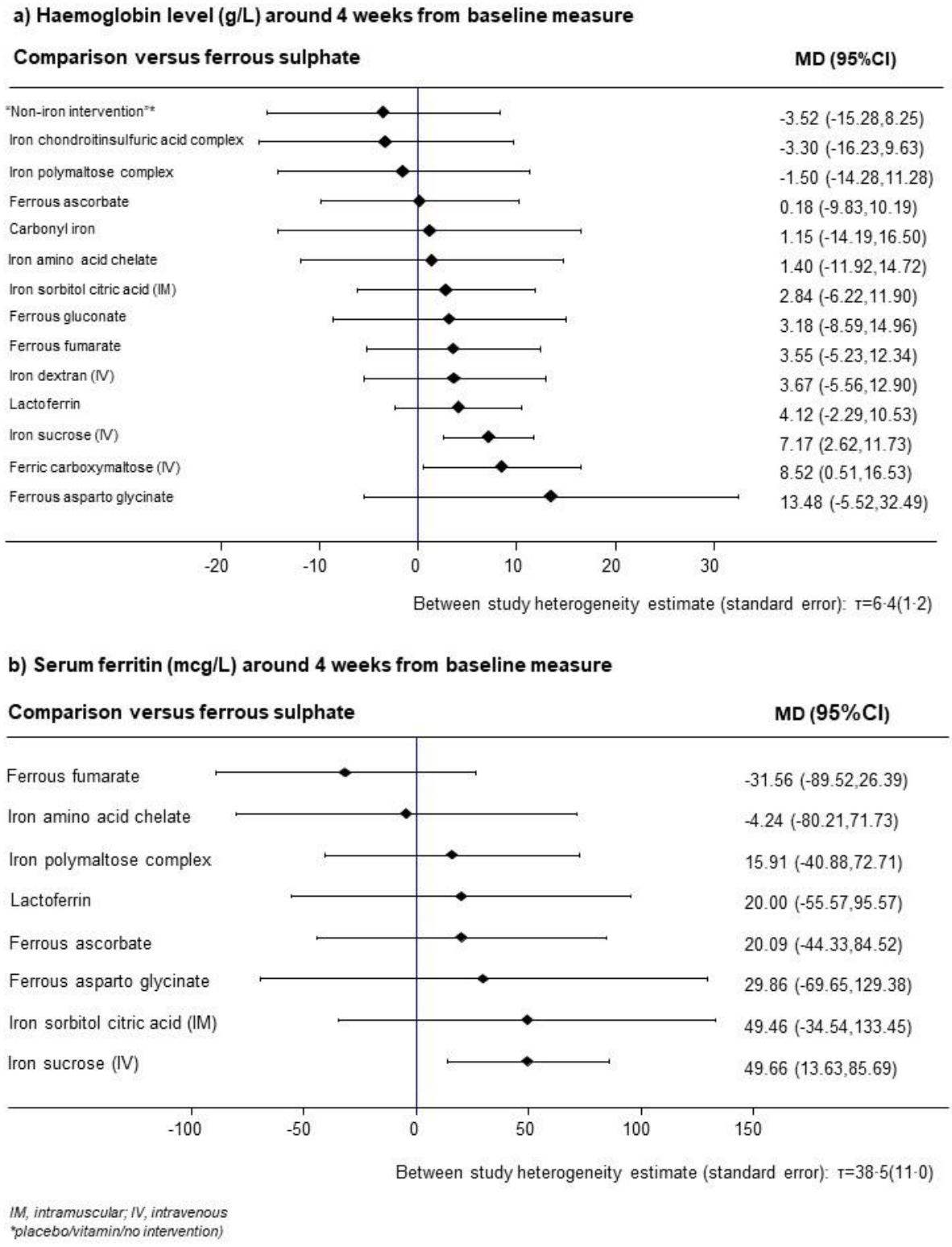


Figure 3. The relative effect of evaluated preparations in comparison to ferrous sulphate on haemoglobin levels and serum ferritin around four weeks from baseline



IM, intramuscular; IV, intravenous
**placebo/vitamin/no intervention)*

Appendix

Appendix 1 Analysis plan

Study title	**Iron treatments (Fe) in Reproductive age women with Iron Deficiency Anaemia (FRIDA): a systematic review with network meta-analysis of randomised controlled trials**

1. Introduction

1.1. Clinical background

Iron deficiency is the commonest nutritional deficiency worldwide. Women of reproductive age are more prone to iron deficiency due to the i) regular loss of blood secondary to the menstrual cycles ii) the increased iron demands of pregnancy and childbirth and iii) physiological differences in iron metabolism as compared to men. Iron deficiency is a progressive process, where the body's iron stores move from being replete to deficient to absent. Absent iron stores lead to a reduction in haemoglobin, which termed anaemia. Anaemia can also be caused by other nutritional deficiencies (vitamin B12 and folate) and structural changes in haemoglobin (termed haemoglobinopthies including thalassemia and sickle cell disease), which are not included in this review.

1.2. Overall study design

Study Design: Network Meta-Analysis (NMA) of randomised controlled trials (RCTs)
Interventions/Comparator: Iron treatment in any formulation, regime and form of administration compared to other iron treatment, placebo, vitamin or mineral supplement, or no treatment.

1.3. Purpose of the analysis plan

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the main outputs of Iron treatments (Fe) in Reproductive age women with Iron Deficient Anaemia (FRIDA) study. Any exploratory, post-hoc or unplanned analyses will be clearly identified in the respective study analysis report.

The following guidelines were reviewed in preparation for writing this document:

1. Study protocol (PROSPERO CRD42018100822)
2. Reporting guidelines PRISMA-NMA (1)

1.4. Review team

Dr Ewelina Rogozinska, Queen Mary University of London
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Prof Javier Zamora, Queen Mary University of London; Hospital Universitario Ramón y Cajal
Prof Khalid S Khan, Queen Mary University of London, UK
Prof Shakila Thangaratinam, Queen Mary University of London, UK

Ewelina Rogozińska, Jahnavi Daru, Rui Wang, Carlos Saborido and Javier Zamora were primarily responsible for writing the Statistical Analysis Strategy. Ewelina Rogozińska will be responsible for writing the statistical software syntax (code) that subsequently will be verified by Carlos Saborido. Ewelina Rogozinska will implement the statistical strategy at the point of analysis.

2. Study objectives

2.1. Primary objective

To compare the relative effectiveness of different iron preparations offered to women of reproductive age with iron deficiency anaemia on haemoglobin levels within three distinctive populations: i) menstruating, ii) pregnant, and iii) postpartum women.

2.2. Secondary objective

To compare different iron preparations offered to women of reproductive age women with iron deficiency anaemia based on their effect on serum ferritin levels and side effects profile within three distinctive populations: i) menstruating, ii) pregnant, and iii) postpartum women.

3. Outcome measures

3.1. Primary outcome(s)

Haemoglobin (Hb) level as reported in the eligible trials. The preference will be towards Hb post-treatment levels, however we will also collect Hb level reported as mean change from baseline and/or achievement of pre-defined Hb threshold.

3.2. Secondary outcome(s)

Serum ferritin (SF) level as reported in the eligible trials. The preference will be towards SF post-treatment levels, however we will also collect SF level reported as mean change from baseline and/or achievement of pre-defined SF threshold.
Any adverse reaction to the treatment collected, will be categorised as severe and non-severe. If the data permit, we will attempt to collect data on following outcomes: death, quality of life, infection, admission to the hospital, and need for blood transfusion.

4. Identification of relevant studies

5.1. Literature search

We will search Cochrane Central Register of Controlled Trials (CENTRAL) to identify studies on effectiveness of iron treatments (any treatment versus any other treatment, placebo, vitamin supplementation or no treatment) in women of reproductive age group. Where required, we will either undertake new searches in Medline (via Ovid), Embase, Scopus, Web of Science and SciELO if there are no relevant Cochrane reviews, or update the search to-date for the relevant Cochrane reviews with the literature searches older than one year. We will not apply any language limitations.

For the additional search strategies, we will use the terms listed in the Cochrane reviews combining three main domains: 'women' (pregnant or non-pregnant separately), 'iron deficiency anaemia', and 'randomised control trial' design. The database search will be supplemented with an exploration of grey literature in SIGLE, trial registers (Clinical Trials Gov., ANZCTR, EU Clinical Trial Register, ISRCTN) and general Internet search (Google and Goole Scholar) for any completed trials with published results not identified in the literature search (non-indexed publications).

Two reviewers will independently evaluate all citations and studies against inclusion criteria. In case of disagreement, we will seek the opinion of a third reviewer. We will develop a list of all evaluated studies with reasons for exclusion for studies considered as not meeting the inclusion criteria.

5.2. Inclusion and exclusion criteria

We will include RCTs with randomisation on a cluster or individual level that included women of reproductive age with iron deficiency anaemia. We will exclude women with known chronic conditions, which likely influence laboratory blood parameters, e.g. chronic kidney disease or those with cancer. The RCTs have to evaluate one or more of iron-based preparation compared with another iron preparation or other intervention (placebo, no treatment, or individual vitamin or mineral supplement). We will exclude all studies where iron preparation is unclear and cannot be classified. The studies will be grouped into those that recruited menstruating, pregnant or postpartum women, and the details of inclusion criteria for population and interventions are presented in Table 1.

Table 1 Research question for menstruating, pregnant or postpartum populations.

Group	Components	Description
Menstruating women	Population	• Any women with diagnosed IDA not caused by a chronic condition
	Intervention/ Comparator	• Iron treatment in any format, regime and form of administration compared to other iron treatment, placebo, vitamin supplement or no treatment. • We will also include studies with blood transfusion and erythropoietin • Exclude studies where iron therapy is given concomitantly with treatments for heavy menstrual bleeding such as hormone treatments, contraception, the Mirena coil, and radiological and surgical treatments
Pregnant	Population	• Women with at any stage of pregnancy with diagnosed IDA not caused by a chronic condition.
	Intervention/ Comparator	• Iron treatment in any format (a minimum of 60mg of elemental iron prescribed) (2), regime and form of administration compared to other iron treatment, placebo, vitamin supplement or no treatment. • We will exclude studies evaluating erythropoietin, micronutrient or multivitamin supplements, or with blood transfusion as an intervention.
Postpartum	Population	• The postpartum period up to 6 weeks after delivery. We assume that anaemia in the postpartum population is due to iron deficiency, unless otherwise stated in the study.
	Intervention/ Comparator	• Iron treatment in any format, regime and form of administration compared to other iron treatment, placebo, vitamin supplement or no treatment.

5. Data extraction and management

We will develop separate Data Extraction Forms (DEF) for all three populations. The DEF will be piloted on five to ten eligible studies. Two researchers will extract data from the included studies independently. Any discrepancies between their choices will be resolved by consensus with input from a third investigator.

5.1. Population characteristics

From all studies regardless of the subpopulation, we will collect following information about women's characteristics: age, ethnicity, baseline intake of iron (if available), baseline Hb and serum ferritin levels.

5.1.1. For women of reproductive age

i. Increased demand for iron (heavy menstrual bleeding, elite athletes, etc.)

ii. Presence of relevant to iron metabolism co-morbidities

5.1.2. For pregnant women

i. Single or multiple gestation

ii. Pre-existing haemoglobinopathies
iii. Obstetric risk factors for haemorrhage

5.1.3.For postnatal women

i. Increased demand for iron (postpartum haemorrhage)
ii. Women receiving donor blood transfusion
iii. Presence of relevant to iron metabolism co-morbidities

For women receiving intravenous iron we will additionally collect information on baseline weight as intravenous iron dosages are calculated according to the participant's baseline Hb level and weight.

5.2. Outcome data

For continuous outcomes, we will extract values and the measures of their variances as given by study authors at the end of the intervention (final values and mean changes from baseline).

For binary outcomes, we will extract number of events and number of participants in a given arm: a) as reported by the study authors for a given analysis; b) as number of participants randomised to a given intervention arm.

5.3. Risk of bias (quality) assessment

The quality of RCTs will be assessed using the approach recommended by the Cochrane risk of bias (version 1.0). (3)

5.4. Data coding and storage

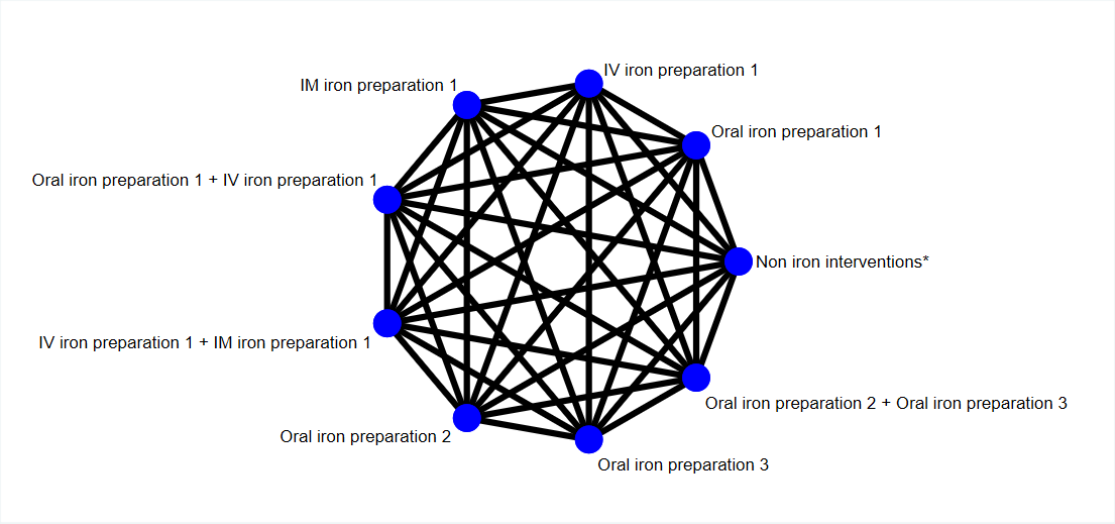
All extracted data will be crosscheck and coded in a uniform way, as described below.

5.4.1. Iron-based interventions

In the first instance, the treatments will be classified by the route of administration and their preparation (Figure 1). We anticipate variability in dose of elemental iron across the included studies. Furthermore, total dose of iron provided intravenously (IV) or intramuscularly (IM) is calculated according to starting Hb level and individual weight. We will, therefore, collect information on frequency, and total daily dose of elemental iron. From studies where iron was provided via IV/IM, we will collect information on women's baseline Hb level (average) and weight (average). The information will be cross tabulate and their comparability assessed across the studies. In case of extreme differences in the doses across the studies, we will explore their impact on the pooled effect in the pair-wise meta-analyses and report this as a limitation of our work.

5.4.2. Multiple iron-interventions

Studies with an arm where two types of iron preparations are both used will be treated as separate node (Figure 1).



IV, intravenous; IM, intramuscular;*placebo, no intervention, vitamins and/or minerals

Figure 1 Conceptual network of iron preparations used to treat iron deficient anaemia

5.4.3.Iron and concomitant interventions

In the first instance we will assume no substantial impact of concomitant, non-iron interventions (vitamins and/or minerals). This assumption will at a later stage be examined further in sensitivity analyses. In multiarm-design trials containing study arms of iron preparations with and without concomitant interventions (vitamin and/or mineral) we will combine data into one group (arm) (means and their variances, events and group size) using available and acceptable methods. (4) We will keep a record of any data transformations.

5.4.4. Non-iron arms

The arms containing placebo, no intervention, vitamins and/or minerals used as comparators will be all labelled as “non-iron treatments”. In multiarm-design trials where a separate placebo and vitamin and/or mineral were used we will combine data into one group (means and their variances, events and group size) using available and acceptable methods. (4) We will keep a record of any data transformations.

5.4.5. Adverse events

We will code adverse events as sever and non-sever following below principles:

a) **Severe:** are those adverse reactions requiring hospital admission, significant morbidity and/or death.

b) **Non-severe**: all other reported adverse reactions (e.g. diarrhoea, constipation, nausea and vomiting, etc.).

5.4.6. Transformation of continuous outcome measures

Data for continuous outcomes for which the measurement variance is reported as standard error will be recalculated to standard deviations using standard equation. (4) For studies where mean values are given without measurement variances, we will follow the approach proposed in the Cochrane Handbook (4). The values reported as median and interquartile ranges (IQR) will be extracted from the literature but not used in the meta-analysis. We will keep a record of any data transformations.

5.4.7. Assumption of missingness for binary outcomes

We will not make any assumptions regarding data missingness and all the analyses will be performed on available case-bases. Potential impact of missing outcome data will be addressed in sensitivity analysis for attrition bias.

6. Strategy for data synthesis

Our main goal is to construct networks comparing all iron preparation reported in included trials in the three pre-defined populations: menstruating women, pregnant and postnatal women. In our work we will follow the best practice recommended for the frequentist approach to network meta-analysis. (5) All analyses will be performed using STATA 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). (6)

6.1. Assessment of transitivity across treatment comparisons

In each population, we will cross-tabulate and inspect baseline characteristics to evaluate the presence of clinical heterogeneity and validity of transitivity assumption. We will visually inspect the distribution of potential effect modifiers such as specified in section 5.1.

6.2. Effect measures

The default effect estimate for continuous measures, will be weighted mean difference (WMD), and for dichotomous odds ratio (OR). We will report both with a respective 95% confidence interval (CI). Our goal is to maximise the number of available for inclusion in the meta-analysis, therefore if any of the effectiveness outcomes (Hb or SF) will be reported as a dichotomous measure, we will assess the possibility of using recognised methods to convert the dichotomous effect measure (OR) to standardised mean difference (SMD). (7) If such a scenario occurs, the reported effect measure will be SMD. The effect estimate will be also presented as SMD if the scales, on which outcomes were measured, across the studies will vary.

6.3. Pair-wise meta-analysis

In the first instance, we will visually inspect the direction of the effect estimates in the direct evidence for each comparisons to assess the feasibility of their pooling in a meta-analysis. If there will be only a single trial reporting data for a given comparison, we will use a fixed effects model to estimate the

effect. Where two or more studies contribute the data, the default will be a random-effects model with restricted maximum likelihood. The statistical heterogeneity will be measured using I^2 statistic and Tau. (8) For continuous outcomes we will report the number of studies that reported median and IQR, and could not be incorporated into the analysis.

6.3.1. Method for handling centre and cluster effects within each trial

Cluster-randomised trials will be incorporated in the pair-wise analyses providing the Inter-Cluster Correlation coefficients are reported.

6.3.2. Adverse events

In case of our intial approach to comparing saftety profile will deem not feasible. We will perform a synthesis of adverse events (9) for the top three interventions identified in the network meta-analysis for the main outcome (Hb) and in the placebo (or no intervention) arms.

6.3.3. Dealing with timing-related issues

Based on the finding of previous research (10-12), we anticipate challenges caused by varying outcome measurement time and treatment duration. We consulted a panel of clinical experts (obstetric haematologists) - independent from this work - to guide our decisions on this matter and ensure clinical relevance. Consequently, we decided what follows:

i. We will collect on the gestational age at inclusion and record the timing of outcome measurement from baseline.
ii. The analysis will performed for the most frequently reported time point and its clinical relevance discussed with the clinical experts
iii. Additionally, if possible, we will perform a sensitivity analysis using all available data in a multivariate network meta-analysis where the timing of a measurement will be incorporated as a covariate.

6.4. Network meta-analysis

6.4.1. Setting up network

For each combination of population and outcome, we will assess feasibility of performing network meta-analysis following subsequent steps:

i. Evaluate the availabilty of data for each comparisons in a pair-wise meta-analysis and distribution of relevant baseline and study-level characteristics
ii. Generate and inspect geometry of the network for its connectivity

The node with the **not-active interventions** (e.g. placebo) will be set as a reference treatment.
If the effect estimates across the studies in the pair-wise meta-analysis will be highly heterogenous (substantial heterogeneity as per Cochrane definition) or network poorly connected, we will refrain from performing network meta-analysis and report only the findings of the pair-wise meta-analysis.

6.4.2.Network meta-analysis

The network meta-analysis will be performed using a multivariate methods following frequentist approach as implemented in network routine in Stata (13, 14) fitting a treatment contrast model with assumption of a common heterogeneity for all comparisons.
We assume that within all three populations (menstruating, pregnant and postpartum women), any woman from the included trials could be equally likely randomised to any other iron treatment. Hence, in the first instance the network meta-analysis will fitted under assumption of consistency. (13)

Testing for consistency
Consistency between direct and indirect sources of evidence will be statistically assessed locally (i.e. for all the closed loops in the network) and globally. The local consistency will be assessed by side-splitting approach (15-17), and the global using design-by-treatment interaction model. (18) If the consistency factors denote its lack, the distribution of effect modifiers within the loop will be explored. At any stage of the network meta-analysis, the transitivity assumptions will be evaluated conceptually for all indirect comparisons to derive valid network meta-analysis estimates.

6.4.3. Ranking treatments

The relative ranking of treatments will be presented in the form of the surface under the cumulative ranking (SUCRA) probabilities for the treatment achieving the highest value of the outcome measure for the effectiveness data, and the lowest value for the adverse events. We will also generate a mean rank for each intervention.

6.4.4. Presentation of the findings

For each model we will generate:

a) Graph with network map
b) Overview of pair comparisons by direct, indirect and mixed (network) evidence.
c) Contribution matrix (study by intervention) showing borrowing of strength from individual studies for each intervention
d) Overview of treatment effects for all interventions in comparison to a common comparator (no iron)
e) Ranking of interventions, mean rank and SUCRA

All information will be collated in the summary of findings tables for network meta-analysis.

6.5. Sensitivity analyses

6.5.1. Secondary models

As a secondary approach we will rank interventions using alternative way of grouping interventions base on a) rout of iron administration (any oral, any IV, any IM); and b) iron salt type combined with route of administration (ferric salts, ferrous salts, lactoferrin).

We will also attempt to apply a multivariate model using all available data and including time of outcome measurement as a covariate.

6.5.2. Subgroup comparison

For the pregnant population we plan a subgroup analyses for the main outcome by country income status according to the World Bank classification (low and middle-income vs high income).

6.5.3. Sensitivity analyses

We will explore the impact of the following factors:

Study quality

We will use CINeMA software (19, 20) to evaluate the confidence in the findings from the main network meta-analysis for Hb levels evaluated around 4 weeks from baseline measure, and interventions treated as individual preparations.

Publication date

We will limit the studies in the main analysis only to those published after year 2000.

Concomitant minerals & vitamins

We will remove arms and studies included in the main analysis were the iron treatment was provided with minerals and/or vitamins such as folic acid, vitamin C, or vitamin B.

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Appendix 2 Details of the methods

Eligibility criteria

We excluded trials:

- comparing different dosage regimens of the same iron preparation e.g. ferrous sulphate 200 mg of elemental iron versus 400 mg of elemental iron (excluded as we compared different types of iron preparations not the amount of elemental iron they contained);
- with erythropoietin or blood transfusion;
- with micronutrient or multivitamin supplements were evaluated as treatment option; however, we allowed trials where individual vitamins such as folic acid, vitamin B12, B2, C or zinc were given alongside iron preparation;
- study arms included vitamin A;
- studies with outdated iron preparations.

Study identification

Databases searched in Cochrane reviews

1. Revirez et al. 2011 (1)

The Cochrane Pregnancy and Childbirth Group's Trials Register (7 June 2011), CENTRAL (2011, Issue 5), PubMed (1966 to June 2011), the International Clinical Trials Registry Platform (ICTRP) (2 May 2011), Health Technology Assessment Program (HTA) (2 May 2011) and LATINREC (Colombia) (2 May 2011).

2. Peña-Rosas et al. 2015 (2)

The Cochrane Pregnancy and Childbirth Group's Trials Register (10 January 2015), the WHO International Clinical Trials Registry Platform (ICTRP) (26 February 2015)

Databases searched for period 2011 to July 2018, and then 2018 to February 2021

- Medline (via Ovid),
- Embase,
- Scopus,
- Web of Science
- Scientific Electronic Library Online (this database was not searched between 2018 and February 2021 due to access issues)

Clinical Trial registers searched for period 2011 to July 2018

- Clinical Trials Gov (also searched between 2018 and February 2021)
- Australian New Zealand Clinical Trials Registry,

- European Union Clinical Trial Register,
- International Standard Randomised Controlled Trial Number registry

Data collection

We extracted data on age, intake of iron, baseline haemoglobin and serum ferritin levels, gestation (single or multiple), gestational age at inclusion, presence of pre-existing haemoglobinopathies, and obstetric risk factors for haemorrhage. We also recorded whether the trials were conducted in areas where parasitic infections are endemic. For trials administering iron intravenous or intramuscularly, we additionally collected data on women's weight as this is required to calculate the total dose of iron. (3,4) For treatment characteristics we collected information on type of iron preparation, route of administration, details of their administration (e.g. how many tablets per day were taken), and the total daily dose of elemental iron (mg).

Additional Analyses

As a secondary approach, the interventions were grouped by:

- **route of administration**: oral, intravenous, intramuscular with lactoferrin, iron amino acid chelate and arms with "no iron preparation" kept separately. Lactoferrin was kept as a separate oral intervention, being a protein from the transferrin family, increasing the uptake of available iron, not a type of iron salt. (5) While iron amino acid chelate is a separate type of oral iron designed to pass through the GI tract without being altered. (6)
- **route of administration and type of iron salt:** oral ferric or oral ferrous salt, intravenous ferric, intramuscular ferric salt. Lactoferrin, iron amino acid chelate and arms with "no iron preparation" kept separately.

In the analyses with a secondary approach to grouping of iron preparations, we used "non-iron intervention" as the reference arm. As in the secondary approach due to broad grouping of preparations it was not possible to use ferrous sulphate (oral ferrous salt) as a reference.

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Appendix 3 Search strategy

Medline via Ovid

Item	Term
1	Pregnancy/
2	pregnan*.af.
3	Gravidity/
4	gravid*.af.
5	gestation*.af.
6	Pregnant Women/
7	pregnant wom#n.af.
8	(child adj3 bearing).af.
9	childbearing.af.
10	matern*.af.
11	antepartum.ab,ti.
12	antenatal.ab,ti.
13	**OR/1-12**
14	**exp Iron Deficiency Anemia/**
15	Hypochromic.af.
16	(iron deficien* OR iron-deficien*).af.
17	microcytic.af.
18	Sideropenic.af.
19	Sideroblastic.af.
20	**OR/15-19**
21	(anaemia OR anemia).af.
22	20 adj 21
23	Ferritin/
24	(Ferriprive OR ferritin* OR isoferritin*).af.
25	**14 OR 20 OR 22 OR 23 OR 24**
26	exp Randomized Controlled Trial/
27	randomized controlled trial.pt.
28	controlled clinical trial.pt.
29	randomized.ab.
30	placebo.ab.
31	clinical trials as topic.sh.
32	randomly.ab.
33	clinical trials as topic.sh.
34	trial.ti.
35	**OR/26-34**
36	**13 AND 25 AND 35**
37	exp Animals/
38	(rat$ or mouse or mice or hamster$ or animal$ or dog$ or cat$ or bovine or sheep or lamb$).af.
39	**37 OR 38**
40	Humans/
41	human$.tw,ot,kf.
42	**40 OR 41**
43	**39 NOT (39 and 42)**
44	**36 NOT 43**

Appendix 4 Characteristics of included studies and iron preparations

1. Characteristics of included studies

a) Data from studies contributing to the network meta-analysis for haemoglobin (n=30)

Study ID	Country name	Comparisons	Haemoglobin level (g/L)	Weight (kg)	Gestational age at inclusion (trimester)	Pre-existing health problems	Sample size
Pregnancy Type: Singleton							
Arzoo 2020	Bangladesh	Ferrous sulphate	79.7	NR	Second to Third	no	150
		Iron sucrose (IV)	79.6				
Bayoumeu 2002	France	Ferrous sulphate	97	53	Second	no	50
		Iron sucrose (IV)	96	55			
Bhavi 2017*	India	Ferrous fumarate	91	NR	NR	no	200
		Iron sucrose (IV)	89				
		No intervention / Placebo	126				
Breymann 2016	Switzerland	Ferrous sulphate	99	57.4	Second to Third	no	247
		Ferric carboxymaltose (IV)	98	59.3			
Dalal 2018*	India	Ferrous sulphate	84.2	NR	Third	no	150
		Iron sucrose (IV)	84				
Deeba 2012*	India	Iron ferrous ascorbate	79	NR	Third	no	200
		Iron sucrose (IV)	79				
Digumarthi 2008*	India	Ferrous fumarate	81	NR	NR	no	30
		Iron sucrose (IV)	81				

Study ID	Country name	Comparisons	Haemoglobin level (g/L)	Weight (kg)	Gestational age at inclusion (trimester)	Pre-existing health problems	Sample size
Gupta 2014*	India	Ferrous sulphate	79	NR	Third	no	100
		Iron sucrose (IV)	78				
Nanthini 2017	India	Iron sorbitol citric acid (IM)	80	56	Second	no	127
		Iron sucrose (IV)	80	56			
Nappi 2009	Italy	Lactoferrin	101	NR	NR	no	100
		Ferrous sulphate	101				
NCT00746551	Thailand	Ferrous fumarate	NR	50.2	Third	NR	80
		Iron sucrose (IV)	NT	48.1			
Neeru 2012	India	Ferrous fumarate	98	NR	Second	unclear	100
		Iron sucrose (IV)	92				
Rajwani 2020	India	Iron sucrose (IV)	78.9	NR	Second to Third	unclear	160
		Ferric carboxymaltose (IV)	78				
Rezk 2016	Egypt	Lactoferrin	80	NR	Second	no	200
		Ferrous sulphate	82				
Tariq 2015	Pakistan	Iron dextran (IV)	87	NR	Second to Third	no	180
		Iron sucrose (IV)	90				
Santiago 2020*	Philippines	Iron sucrose (IV)	99.7	NR	Second	no	48
		Iron amino acid chelate	101.2				

Study ID	Country name	Comparisons	Haemoglobin level (g/L)	Weight (kg)	Gestational age at inclusion (trimester)	Pre-existing health problems	Sample size
Pregnancy Type: Mixed							
Abhilashini 2014	India	Ferrous sulphate	72	50	Third	no	100
		Iron sucrose (IV)	69	56			
Aggarwal 2021*	India	Ferrous sulphate	60	55.9	Third	unclear	50
		Iron sucrose (IV)	63	54.5			
Dhanani 2012*	India	Iron sorbitol citric acid (IM)	83	46	Second	no	60
		Iron sucrose (IV)	76	46			
Fochi 1985	Italy	Ferrous sulphate	110	NR	Second	no	69
		Iron chondroitinsulfuric acid	106				
Gawai 2020	India	Lactoferrin	90.3	NR	Second to Third	unclear	100
		Ferrous sulphate	91.3				
Jose 2019	India	Iron sucrose (IV)	87	57	Third	no	100
		Ferric carboxymaltose (IV)	86	57			
Kamdi 2015*	India	Iron ferrous ascorbate	83	44.4	NR	unclear	73
		Ferrous asparto glycinate	84	44.5			
Kochhar 2013*	India	Ferrous sulphate	76	51	Second to Third	Infectious diseases (other)	100
		Iron sucrose (IV)	77	53			
Ortiz 2011	Columbia & Argentina	Ferrous sulphate	99	NR	Second	unclear	80
		Iron polymaltose complex	96				

Study ID	Country name	Comparisons	Haemoglobin level (g/L)	Weight (kg)	Gestational age at inclusion (trimester)	Pre-existing health problems	Sample size
Paesano 2010*	Italy	Lactoferrin	100	NR	NR	no	75
		Ferrous sulphate	100				
Rudra 2016*m	India	Ferrous ascorbate	79	NR	Third	unclear	200
		Iron sucrose (IV)	78				
Sagaonkar 2009	India	Ferrous fumarate	85	43	Second	unclear	150
		Carbonyl iron	84	43			
Singh 2012	India	Iron sorbitol citric acid (IM)	68	NR	Second	unclear	100
		Iron sucrose (IV)	65				
Symonds 1969	Australia	Ferrous sulphate	101	NR	NR	unclear	100
		Iron Ferrous Gluconate	101				
		Iron dextran (IV)	103				
		No intervention / Placebo	103				

IV, intravenous; IM, intramuscular

**contributing data to the network meta-analysis for serum ferritin*

b) Data <u>not</u> contributing to the network meta-analysis for haemoglobin (n=23)

Study ID	Country name	Comparisons	Haemoglobin level (g/L)	Weight (kg)	Gestational age at inclusion (trimester)	Pre-existing health problems	Sample size
Pregnancy Type: Singleton							
Al 2005*	Turkey	Iron polymaltose complex	98	58	Third	no	90
		Iron sucrose (IV)	99	56			
Hayat 2019	India	Iron dextran (IM)	87	NR	First	no	198
		Iron sucrose (IV)	90				
Khalafallah 2010	Australia	Ferrous sulphate	107	75	Second	no	200
		Iron polymaltose (IV) followed by Ferrous sulphate	109	73			
Komolafe 2003	Nigeria	Ferrous sulphate	NR	NR	Second	infectious diseases (other)	60
		Iron dextran (IM)					
Kumar 2005	India	Ferrous sulphate	99	NR	Second	infectious diseases (other)	220
		Iron sorbitol citric acid (IM)	96				
Sharma 2004	India	Ferrous sulphate	96	NR	Second	infectious diseases (other)	254
		Iron dextran (IM)	94				
Van Eijk 1978	Netherlands	Ferrous sulphate	82	NR	First	no	30
		No intervention / Placebo	82				

Study ID	Country name	Comparisons	Haemoglobin level (g/L)	Weight (kg)	Gestational age at inclusion (trimester)	Pre-existing health problems	Sample size
Pregnancy Type: Mixed							
Al Momen 1996	Saudi Arabia	Iron polymaltose complex	98	58	Third	no	100
		Iron sucrose (IV)	99	56			
Borg 2020	India	Lactoferrin	NR	NR	NR	unclear	98
		Ferrous sulphate					
Darwish 2017	Egypt	Ferrous fumarate	82	NR	Second	no	66
		Iron dextran (IV)	56				
Darwish 2018	Egypt	Lactoferrin	86	NR	Second	no	120
		Iron dextran (IV)	82				
Han 2011	China	Ferrous sulphate	100	NR	Second	unclear	153
		NaFeEDTA	100				
		Placebo	102				
Ma 2010	China	Ferrous sulphate	99	NR	Second	unclear	164
		Placebo	102				
Mehta 2014	India	Ferrous fumarate	67	NR	Second to Third	no	150
		Iron sucrose (IV)	67				
Menendez 1994	Gambia	Ferrous sulphate	100	55	Second	Yes (heamoglobinopathies)	500
		Placebo	101	55			
Preziosi 1997	Nigeria	Ferrous betainate	NR	NR	Third	NR	197
		Placebo					

Study ID	Country name	Comparisons	Haemoglobin level (g/L)	Weight (kg)	Gestational age at inclusion (trimester)	Pre-existing health problems	Sample size
Samsudin 2020	Malaysia	Iron sucrose (IV)	84	55.8	Second to Third	no	40
		Iron dextran (IV)	86	62.8			
Simmons 1993	Jamaica	Ferrous sulphate	101	62	Second	unclear	376
		No intervention	99	60			
Singh 1998	Singapore	Ferrous fumarate	86	NR	NR	unclear	100
		Iron polymaltose complex	81				
Suharno 1993	Indonesia	Ferrous sulphate	103	50	Second	unclear	305
		Placebo	103	49			
Sun 2010	China	Ferrous sulphate	100	NR	Second	unclear	186
		Placebo	101				
Tanumihardjo 2002	Indonesia	Ferrous sulphate	112	46.8	Second	unclear	27
		Placebo	113	46.8			

IV, intravenous; IM, intramuscular; NR, not reported

**contributing data to the network meta-analysis for serum ferritin*

2. Characteristics of iron preparations in the included studies

a) Data from studies contributing to the network meta-analysis for haemoglobin (n=30)

Intervention	Study ID	Preparation dose (mg)	Frequency	Total daily dose (mg)	Concomitant	Treatment duration (weeks)
Oral iron preparations						
Ferrous asparto glycinate	Kamdi 2015	100 e.	1xday	100 e.	Folic acid	4
Carbonyl iron	Sagaonkar 2009	NR	1xday	100 e.	Folic acid, vitamin B12, zinc	12
Iron amino acid chelate	Santiago 2019	30 e.	2xday	60 e.	NR	12
Iron chondroitin-sulphuric acid	Fochi 1985	NR	3xday	90 e.	NR	7.1 (50 days)
Iron polymaltose complex	Ortiz 2011	100 e.	2xday	200 e.	NR	12.9
Ferrous ascorbate	Deeba 2012	100 e.	2xday	200 e.	Folic acid	8
	Kamdi 2015	100 e.	1xday	100 e.	Folic acid	4
	Rudra 2016	100 e.	2xday	200 e.	Folic acid	12
Ferrous fumarate	Bhavi 2017	100 e.	2xday	200 e.	Folic acid	4
	Digumarthi 2008	300	2xday	100 e.	Folic acid	NR
	Nerru 2012	300	NR	100 e.	NR	NR
	NCT00746551	NR	3xday	200 e.	Folic acid	3
	Sagaonkar 2009	152	2xday	100 e.	Folic acid, zinc	12
Ferrous gluconate	Symonds 1969	NR	3xday	108 e.	NR	min. 8

Intervention	Study ID	Preparation dose (mg)	Frequency	Total daily dose (mg)	Concomitant	Treatment duration (weeks)
Ferrous sulphate	Abhilashini 2014	200	3xday	180 e.	NR	~ 8
	Aggarwal 2012	200	3xday	180 e.	NR	4
	Arzoo 2020	200	3xday	180 e.	NR	9
	Bayoumeu 2002	80	3xday	240 e.	Folic acid	4
	Breymann 2016	100	2xday	200 e.	NR	12
	Dalal 2018	100 e.	2xday	200 e.	Albendazole	NR
	Fochi 1985	NR	1xday	105 e.	NR	7.1 (50 days)
	Gawai 2020	200	2xday	120 e.	NR	8
	Gupta 2014	200	3xday	180 e.	NR	4
	Kochhar 2013	200	3xday	180 e.	NR	4
	Nappi 2009	520	1xday	100 e.	Folic acid	4
	Ortiz 2011	100	2xday	100 e.	NR	12.9
	Paesano 2010	520	1xday	100 e.	NR	4.3 (30 days)
	Rezk 2016	150	1xday	NR	Folic acid	8
	Santiago 2019	65 e.	2xday	130 e.	NR	12
	Symonds 1969*	525	1xday	105 e.	NR	min. 8

Intervention	Study ID	Preparation dose (mg)	Frequency	Total daily dose (mg)	Concomitant	Treatment duration (weeks)
IV iron preparation						
Iron dextran	Symonds 1969**	20 of iron /ml	5 infusions	100 of iron	NR	NR
	Tariq 2015 (LMW)	NR	Single injection	Target set individually	NR	One day
Iron sucrose	Abhilashini 2014	200	alternate days	Target set individually	NR	Until target reached
	Aggarwal 2012	200	6 infusions, alternate days	Target set individually	Folic acid	10 days
	Arzoo 2020	200	alternate day	Target set individually	NR	Unclear
	Bayoumeu 2002	max of 200	6 infusions, alternate days	Target set individually	Folic acid	3
	Bhavi 2017	200 e.	1xday	Target set individually	Folic acid	Until target reached
	Dalal 2018	200 e.	Consecutive days until dose achieved before delivery	Target set individually	Albendazole	Until target reached
	Deeba 2012	200 e.	NR	Target set individually	NR	Until target reached
	Dhanani 2012	100 e.	Single infusion	200 e.	NR	One day
	Digumarthi 2008	NR	NR	Target set individually	NR	Until target reached
	Gupta 2014	200	Alternate days	Target set individually	NR	Until target reached
	Jose 2019	300	2xweek	max of 600 / week	Mebendazole, folic acid	2
	Kochhar 2013	100	Alternate days	Target set individually	NR	Until target reached
	Nanthini 2017	100 e.	Alternate days	Target set individually	NR	NR
	Neeru 2012***	200	Alternate days	Target set individually	NR	NR

Intervention	Study ID	Preparation dose (mg)	Frequency	Total daily dose (mg)	Concomitant	Treatment duration (weeks)
Iron sucrose (cont.)	NCT00746551	200	3 infusions	max. of 500 / week	NR	3
	Rajwani 2020	200	Alternate days	Target set individually	NR	4
	Rudra 2016	200	Alternate days	max. of 600 / week	Folic acid	3
	Singh 2012	150	Every 3 days	Target set individually	NR	Until target reached
	Tariq 2015	NR	Single infusion	Target set individually	NR	One day
Ferric carboxymaltose	Breymann 2016	1000 - 1500	NR	Target set individually	NR	3
	Rajwani 2020	1000	Single infusion?	Target set individually	NR	One day?
	Jose 2019	max. per sit 1000	3 infusions	Target set individually	Mebendazole, folic acid	Until target reached
IM iron preparation						
Iron sorbitol citric acid	Dhanani 2012	75 e.	4 injections	300 e.	NR	4 days
	Nanthini 2017	100	1xday	NR	NR	NR
	Singh 2012	1.5 ml	1xday	Target set individually	NR	Until target reached
Non-iron preparation						
Lactoferrin	Gawai 2020	250	2xday	500	NR	8
	Nappi 2009	100	2xday	200	Folic acid	4
	Paesano 2010	100	2xday	200	NR	4.3 (30 days)
	Rezk 2016	250	1xday	250	NR	8
No-iron intervention****	Simmons 1993	NR	1xday	N/A	Folic acid	12
	Symonds 1969	N/A	1xday	N/A	NR	min. 8

e., elemental iron; LWM, low molecular weight; NR, not reported
**controlled-release*
***unclear if iron dextran was high or low molecular weight*

****routine oral iron supplementation was withheld during intravenous iron but restarted 1wk post IV treatment*
*****vitamins, placebo or no intervention at all*

b) Data from studies <u>not</u> contributing to the network meta-analysis for haemglobin (n=23)

Intervention	Study ID	Preparation dose (mg)	Frequency	Total daily dose (mg)	Concomitant	Treatment duration (weeks)
Oral preparations						
Ferrous betainate	Preziosi 1997	unknown	1xday	100 e.	NR	~ 12
Ferrous fumarate	Singh 1998	200	3xday	100 e.	NR	12
	Darwish 2017	60 e.	3xday	180 e.	NR	4
Ferrous sulphate	Al Momen 1996	300	3xday	180 e.	NR	NR
	Borg 2020	520	1xday	NR	NR	4
	Han 2011	60	1xday	60 e.	NR	8
	Khalafallah 2010	250	1xday	80 e.	NR	15
	Komolafe 2003	200	3xday	180 e.	Folic acid, vitamin C	NR
	Kumar 2005	100	1xday	100 e.	Folic acid, Mebendzole	19
	Ma 2010	60	1xday	60 e.	Folic acid, vitamin B2	8
	Mehta 2014	400	3xday	360 e.	NR	NR
	Menendez 1994	60	1xday	60 e.	Folic acid	16
	Neogi 2019	100 e.	2xday	200 e.	Folic acid	19
	Sharma 2004	NR	1xday	100 e.	Folic acid	20
	Suharno 1993	60 e.	1xday	60 e.	NR	8
	Sun 2010	60	1xday	60 e.	Folic acid	8

Intervention	Study ID	Preparation dose (mg)	Frequency	Total daily dose (mg)	Concomitant	Treatment duration (weeks)
Ferrous sulphate (cont.)	Tanumihardjo 2002	1.07 mmol	1xday	60 e.	NR	min. 8
	Van Eijk 1978	100	1xday	60 e.	NR	12
Iron polymaltose complex	Al 2005	100	3xday	300 e.	Folic acid	11
NaFeEDTA	Han 2011	60	1xday	60 e.	NR	8
IV and oral preparation						
Ferrous sulphate and iron polymaltose	Khalafallah 2010	250 / NR	1xday / single infusion	80 e. / target set individually	NR	13
IV preparation						
Iron polymaltose	Singh 1998	50	Single infusion	Target set individually	Promethazine	NR
Iron dextran	Darwish 2017 (LMW)	50	Single infusion	Target set individually	NR	One day
	Darwish 2018 (LMW)	50	Single infusion	Target set individually	NR	One day
	Hayat 2019	0.1 ml	Single infusion (6-8h)	Target set individually	NR	One day
	Samsudin 2020 (LMW)	Max 20 mg / kg	Single infusion (4-6h)	Target set individually	NR	One day
Iron sucrose	Al 2005	200 e.	Alternate days	Target set individually	Folic acid	5 days
	Al Momen 1996	200 e.	NR	Target set individually	NR	Until target reached
	Hayat 2019	NR	NR	NR	NR	NR
	Mehta 2014	100	Alternate days	Target set individually	NR	NR
	Neogi 2019	200	NR	Target set individually	Folic acid	Until target reached

Intervention	Study ID	Preparation dose (mg)	Frequency	Total daily dose (mg)	Concomitant	Treatment duration (weeks)
Iron sucrose (cont.)	Samsudin 2020	200	an interval of 1–3 days per week	Target set individually; max 600 mg a week	NR	Until target reached
IM preparation						
Iron dextran	Komolafe 2003*	50	3xweek	Target set individually	Promethazine	Until target reached
	Sharma 2004 (HMW)	250 e.	Three injections (1-month intervals)	Target set individually	Folic acid	12
Iron sorbitol citric acid	Kumar 2005	250 e.	Two injections (4-6weeks interval)	250 e.	Mebendzole	4-6
Non-iron preparation						
Lactoferrin	Borg 2020	100	2xday	200 e.	NR	4
	Darwish 2018	100	2xday	200 e.	NR	4
No-iron intervention**	Han 2011	NA	1xday	NA	NR	8
	Ma 2010	NA	1xday	NA	NR	8
	Menendez 1994	NA	1xday	NA	Folic acid	16
	Preziosi 1997	NA	NR	NA	NR	~ 12
	Suharno 1993	NA	1xday	NA	NR	8
	Sun 2010	NA	1xday	NA	NR	8
	Tanumihardjo 2002	NA	1xday	NA	NR	min. 8
	Van Eijk 1978	NA	NR	NA	NR	12

e., elemental iron; LWM, low molecular weight; NR, not reported
**unclear if iron dextran was high or low molecular weight*
***vitamins, placebo or no intervention at all*

Appendix 5 Pair-wise meta-analysis for comparisons with more than one study available

a) Haemoglobin (g/L)

Comparison (Number of studies)	Number of women	MD	LCI	UCI	τ^2	I^2 (%)	Hb at baseline (g/dL)	Country	Concomitant medication	Total Daily Dose of elemental iron (mg)*	Global risk of bias
IFS vs LAC (4)	**457**	**-4.1**	**-10.3**	**2.09**	**37.6**	**96.6**					
Gawai 2020	100	1.1	-0.98	3.18							
Nappi 2009	*97*	*3.0*	*0.8*	*5.2*			101/101	Italy	FA	100 / NR	Low
Paesano 2010	*60*	*-15.0*	*-20.1*	*-9.9*			100/100	India	NR	100 / NR	High[1]
Rezk 2016	*200*	*-6.8*	*-8.4*	*-5.2*			80/82	India	IFS with FA	90 / NR	High[1,2]
IFS vs IVISU (7)	**695**	**-8.4**	**-13.8**	**-2.9**	**50.2**	**95.7**					
Abhilashini 2014	*100*	*-3.3*	*-6.0*	*-0.6*			72/69	India	NR	180 / NA	Low
Aggarwal 2012	*50*	*-10.4*	*-15.4*	*-5.4*			60/63	India	IVISU with FA	180 / NA	Medium
Arzoo 2020	*150*	*-15.3*	*-17.4*	*-13.2*							
Bayoumeu 2002	*47*	*-1.1*	*-8.4*	*6.2*			97/96	France	FA	240 / NA	Low
Dalal 2018	*150*	*-0.4*	*-3.4*	*2.6*			84/84	India	NR	200 / NA	High[2]
*Gupta 2014**	*100*	*-6.2*	*-8.2*	*-4.2*			79/78	India	NR	180 / NA	Low
*Kochhar 2013**	*99*	*-21.0*	*-24.6*	*-17.4*			76/77	India	NR	180 / NA	Medium
IFF vs IVISU (4)	**305**	**-2.9**	**-5.0**	**-0.8**	**0**	**0**					
NCT00746551	*74*	*-4.0*	*-7.8*	*-0.2*			NR	Thailand	IFF with FA	200 / NA	High[2]
Bhavi 2017	*112*	*0.1*	*-34.1*	*34.3*			91/89	India	FA	200 / NA	Medium
Digumarthi 2008	*30*	*-6.0*	*-12.8*	*0.8*			81/81	India	IFF with FA	100 / NA	Medium
Neeru 2012	*89*	*-1.8*	*-4.6*	*1.0*			98/92	India	NR	100 / NA	Low
IFA vs IVISU (2)	**400**	**-6.6**	**-7.8**	**-5.5**	**0.1**	**10.2**					
Deeba 2012	*200*	*-7.7*	*-11.0*	*-0.54*			79/79	India	IFA with FA	200 / NA	Low
Rudra 2016	*200*	*-6.3*	*-7.5*	*-0.51*			78/79	India	FA	200 / NA	High[2]
IMISCA vs IVISU (3)	**279**	**-4.3**	**-12.3**	**3.8**	**43.7**	**93.6**					
Dhanani 2012	*52*	*5.2*	*-4.5*	*14.9*			83/76	India	NR	NR	High[1]
NRnthani 2017	*127*	*-2.9*	*-5.3*	*-0.6*			80/80	India	NR	NR	Medium
Singh 2012	*100*	*-12.0*	*-14.7*	*-9.4*			68/65	India	NR	NR	High[3]

**additional administration of anti-parasitic tablets*
MD, mean difference; LCI, lower confidence interval; UCI, upper confidence interval; Hb, Haemoglobin; NR, not reported, NA, not available
IFS, ferrous sulphate; LAC, lactoferrin; IVISU, intravenous iron sucrose; IMISCA, intramuscular iron sorbitol citric acid; IFF, ferrous fumarate; IFA, ferrous ascorbate; FA, folic acid;
***Global risk of bias**: 1. Incomplete outcome data, 2. Blinding of participants and personnel, 3. Selective reporting*

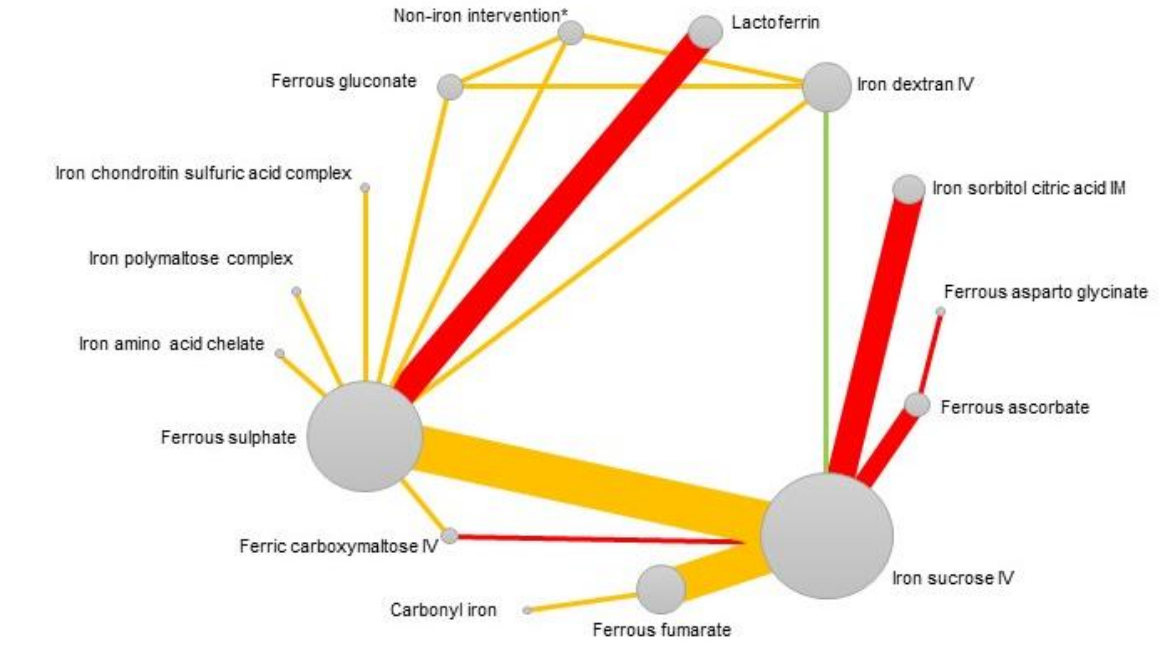
b) Serum ferritin (mcg/L)

Comparison (Number of studies)	Number of women	MD	LCI	UCI	τ^2	I^2 (%)	Hb at baseline (g/L)	Country	Concomitant medication	Total Daily Dose of elemental iron (mg)	Global risk of bias
IVISU vs IFA (2)	**400**	**-29.43**	**-45.36**	**-13.49**	**129.8**	**98.2**					
Deeba 2012	*200*	*-37.69*	*-41.89*	*-33.49*			79/79	India	IFA with FA	NR / 200	Low
Rudra 2016	*200*	*-21.43*	*-22.36*	*-20.50*			78/79	India	FA	NR / 200	High[2]
IFS vs IVISU (4)	**400**	**-55.01**	**-77.82**	**-32.2**	**297.6**	**98**					
Aggarwal 2012	*50*	-134.7	-156.63	-112.77			60/63	India	IVISU with FA	180 / NA	Medium
Dalal 2018	*150*	-36.96	-45.93	27.99			84/84	India	NR	200 / NA	High[2]
*Gupta 2014**	*100*	-23.49	-25.16	-21.82			79/78	India	NR	180 / NA	Low
*Kochhar 2013**	*100*	-26.40	-31.71	-21.09			76/77	India	NR	180 / NA	Medium
IFF vs IVISU (3)	**216**	**-81.43**	**-118.05**	**-44.81**	**922.5**	**88.3**					
NCT00746551	*74*	-107.8	-125.94	-89.66			NR	Thailand	IFF with FA	200 / NA	High[2]
Bhavi 2017	*112*	-90.23	-113.4	-67.06			91/89	India	FA	200 / NA	Medium
Digumarthi 2008	30	-44.46	-68.55	-20.37			81/81	India	IFF with FA	100 / NA	Medium

**additional administration of anti-parasitic tablets*
MD, mean difference; LCI, lower confidence interval; UCI, upper confidence interval; Hb, haemoglobin; NA, not available
IVISU, intravenous iron sucrose; IFA, ferrous ascorbate; IFS, ferrous sulphate; IFF, ferrous fumarate; FA, folic acid;
***Global risk of bias**: 1. Incomplete outcome data, 2. Blinding of participants and personnel, 3. Selective reporting*

Appendix 6 Risk of bias

a) Quality of evidence in the main network



b) Assessment of risk of bias and indirectness of study population by individual study

Study ID	Random sequence generation	Allocation concealment	Blinding of staff and participants	Blinding of outcome assessor	Incomplete outcome data	Selective reporting of outcomes	Global risk of bias*	Indirectness*
Trials contributing data to the network meta-analysis for haemoglobin								
Abhilashini 2014	Low	Unclear	Low	Low	Low	Low	**Low**	Medium
Aggarwal 2012	Unclear	Low	Unclear	Low	Unclear	Low	**Medium**	Low
Arzoo 2020	Low	Unclear	Unclear	Low	Low	Low	**Medium**	Low
Bayoumeu 2002	Low	Unclear	Low	Low	Low	Low	**Low**	Low
Bhavi 2017	Unclear	Unclear	Low	Low	Low	Low	**Medium**	Low
Breymann 2016	Unclear	Unclear	Low	Low	Low	Low	**Medium**	Low
Dalal 2018	Low	Low	High	Low	Unclear	Low	**High**	Low
Deeba 2012	Low	Low	Low	Low	Low	Low	**Low**	Low
Dhanani 2012	Unclear	Unclear	Low	Low	High	Unclear	**High**	Medium
Digumarthi 2008	Unclear	Unclear	Unclear	Low	Unclear	Unclear	**Medium**	Low
Fochi 1985	Unclear	Unclear	Unclear	Low	Unclear	Low	**Medium**	Low
Gawai 2020	Unclear	Unclear	Unclear	Low	Low	Low	**Medium**	Low
Gupta 2014	Low	Low	Low	Low	Low	Low	**Low**	Low
Jose 2019	Low	Unclear	Low	Low	Low	Low	**Low**	Low
Kamdi 2015	High	High	Low	Low	High	Unclear	**High**	Low
Kochhar 2013	Low	Unclear	Unclear	Low	Low	Low	**Medium**	Low
Nanthini 2017	Unclear	Unclear	Low	Low	Low	Unclear	**Medium**	Low
Nappi 2009	Low	Unclear	Low	Low	Low	Low	**Low**	Low
NCT00746551	Unclear	Unclear	High	Low	Low	Low	**High**	Low
Neeru 2012	Low	Unclear	Low	Low	Low	Low	**Low**	Low

Study ID	Random sequence generation	Allocation concealment	Blinding of staff and participants	Blinding of outcome assessor	Incomplete outcome data	Selective reporting of outcomes	Global risk of bias*	Indirectness*
Ortiz 2011	Low	Unclear	Unclear	Low	Low	Low	**Medium**	Low
Paesano 2010	Unclear	Unclear	Unclear	Low	High	Unclear	**High**	Medium
Rajwani 2020	High	Unclear	Unclear	Low	Low	Unclear	**High**	Low
Rezk 2016	Low	Low	High	Low	High	Low	**High**	Low
Rudra 2016	Low	Unclear	High	Low	Unclear	Unclear	**High**	Low
Sagaonkar 2009	Unclear	Low	Unclear	Low	Low	Low	**Medium**	Low
Santiago 2020	Low	Unclear	Unclear	Low	Low	Low	**Medium**	Low
Singh 2012	Unclear	Unclear	Low	Low	Low	High	**High**	Low
Symonds 1969	Unclear	Unclear	Low	Low	Low	Low	**Medium**	Low
Tariq 2015	Low	Unclear	Low	Low	Low	Low	**Low**	Low
Trials not contributing data to the network meta-analysis for haemoglobin								
Al 2005**	Low	Low	Low	Low	Low	High	-	-
AlMomen 1996	High	Unclear	Low	Low	Low	Unclear	-	-
Borg 2020	Unclear	Unclear	Unclear	Low	Unclear	Unclear	-	-
Darwish 2017	Low	Low	Low	Low	Low	Low	-	-
Darwish 2018	Low	Low	Low	Low	High	Low	-	-
Han 2011	High	Unclear	Unclear	Low	Low	Low	-	-
Hayat 2019	Unclear	Unclear	Unclear	Low	High	Unclear	-	-
Khalafallah 2010	Low	Low	Low	Low	Low	Low	-	-
Komolafe 2003	Low	Unclear	Unclear	Low	Low	Low	-	-
Kumar 2005	Unclear	Unclear	Unclear	Low	High	Unclear	-	-
Ma 2010	High	Low	Low	Low	Low	Low	-	-
Mehta 2014	Unclear	Unclear	High	Low	Unclear	Unclear	-	-
Menendez 1994	High	Unclear	Unclear	Low	Low	Low	-	-
Neogi 2019	Low	Low	High	Low	High	Low	-	-
Preziosi 1997	Low	Unclear	Unclear	Low	Unclear	Unclear	-	-
Samsudin 2020	Low	Low	Unclear	Low	Low	Low	-	-
Sharma 2004	Unclear	Unclear	Low	Low	High	Low	-	-
Simmons 1993	Low	Unclear	High	Low	High	Unclear	-	-
Singh 1998	Unclear	Unclear	Unclear	Low	Low	High	-	-
Suharno 1993	High	Low	Low	Low	Low	Unclear	-	-
Sun 2010	Unclear	Low	Low	Low	Low	Low	-	-
Tanumihardjo 2002	Unclear	Unclear	Unclear	Low	Low	Low	-	-
Van Eijk 1978	Unclear	Unclear	Unclear	Low	Low	Low	-	-

**We created global risk of bias and assessed population indirectness only for trials contributing date to the haemoglobin network meta-analysis;*

***Trial contributing data to network meta-analysis for serum ferritin*

Appendix 7 Detailed network meta-analysis outputs

1. Network summary

	Haemoglobin	Serum ferritin
Number of studies	30	15
Number of women	3243	1396
Number of unique interventions	15	9

2. Network evidence from a consistency model assuming constant heterogeneity variance across all comparisons

a) Haemoglobin (g/L)

Comparisons		Network evidence MD (95% CI)
Experimental	**Comparator**	
Ferrous aspartic glycinate	Ferrous ascorbate	13·3 (-2·9 to 29·5)
Ferrous ascorbate	Iron sucrose (IV)	-7·0 (-16·0 to 2·0)
Ferrous fumarate	Carbonyl iron	2·4 (-10·1 to 15·0)
	Iron sucrose (IV)	-3·6 (-11·1 to 3·9)
Ferrous gluconate	Iron dextran (IV)	-0·5 (-12·3 to 11·3)
	"Non-iron intervention"	6·7 (-5·8 to 19·2)
Ferrous sulphate	Iron amino acid chelate	-1·4 (-14·7 to 11·9)
	Ferrous gluconate	-3·2 (-15·0 to 8·6)
	Iron chondroitin sulphuric acid	3·3 (-9·6 to 16·2)
	Iron polymaltose complex	1·5 (-11·3 to 14·3)
	Iron dextran (IV)	-3·7 (-12·9 to 5·6)
	Ferric carboxymaltose (IV)	-8·5 (-16·5 to -0·5)
	Iron sucrose (IV)	-7·2 (-11·7 to -2·6)
	Lactoferrin	-4·1 (-10·5 to 2·3)
	"Non-iron intervention"	3·5 (-8·3 to 15·3)
Iron dextran (IV)	"Non-iron intervention"	7·2 (-4·6 to 19·0)
Iron sucrose (IV)	Iron dextran (IV)	3·5 (-5·8 to 12·8)
	Ferric carboxymaltose (IV)	-1·3 (-8·9 to 6·2)
Iron sorbitol citric acid (IM)	Iron sucrose (IV)	-4·3 (-12·2 to 3·5)

Between study heterogeneity estimate (standard error): τ=6·4(1·2)

b) Serum ferritin (mcg/L)

Comparisons		Network evidence MD (95% CI)
Experimental	**Comparator**	
Ferrous aspartic glycinate	Ferrous ascorbate	9·8 (-66·1 to 85·6)
Ferrous sulphate	Iron amino acid chelate	4·2 (-71·7 to 80·2)
	Iron polymaltose complex	-15·9 (-72·7 to 40·9)
	Iron sucrose (IV)	-49·7 (-85·7 to -13·6)
	Lactoferrin	-20·0 (-95·6 to 55·6)
Iron sucrose (IV)	Ferrous ascorbate	29·6 (-23·9 to 82·9)
	Ferrous fumarate	81·2 (35·8 to 126·6)
	Iron polymaltose complex	33·7 (-23·0 to 90·5)
	Iron sorbitol citric acid (IM)	0·2 (-75·7 to 76·1)

Between study heterogeneity estimate (standard error): τ=38·5(11·0)

3. Local and global tests of inconsistency

(a) Haemoglobin (g/L)

Treatment comparison		Difference between direct and indirect estimates (SE)*	p-value for inconsistency
IFS	IVIDX	-5.2 (9.7)	0.59
IFS	IVIFCM	-9.5 (8.3)	0.25
IFS	IVISU	8.3 (6.4)	0.20
IFS	NOFE	-10.4 (19.4)	0.59
FASG	IFA	-14.2 (**)	-
ICARB	IFF	-4.7 (**)	-
IFA	IVISU	-7.3 (**)	-
IFF	IVISU	-4.4 (**)	-
IFG	IFS	10.4 (19.4)	0.59
IFG	IVIDX	-10.4 (19.4)	0.59
IMISCA	IVISU	-10.0 (**)	-
IVIDX	IVISU	-5.2 (9.7)	0.59
IVIDX	NOFE	10.4 (19.4)	0.59
IVIFCM	IVISU	-9.5 (8.3)	0.25

FASG, ferrous asparto glycinate; ICARB, carbonyl iron; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)
Global test for inconsistency, p=0.43
**Difference is direct estimate – indirect estimate*
***Not possible to estimate standard error due to network location*

(b) Serum ferritin (mcg/L)

Treatment comparison		Difference between direct and indirect estimates (SE)*	p-value for inconsistency
IFS	IPMCX	-38.0 (61.5)	0.54
IFS	IVISU	38.1 (61.3)	0.54
FASG	IFA	-50.4 (**)	-
IFA	IVISU	-61.6 (**)	-
IFF	IVISU	-18.4 (**)	-
IMISCA	IVISU	-99.1 (**)	-
IPMCX	IVISU	-38.0 (61.5)	0.54

FASG, ferrous asparto glycinate; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IVISU, intravenous iron sucrose; IPMCX, iron polymaltose complex;
Global test for inconsistency, p=0.54
**Difference is direct estimate – indirect estimate*
***Not possible to estimate standard error due to network location*

4. Ranking of iron interventions

a) Haemoglobin

Rank	FASG	IVIFCM	IVISU	LAC	IVIDX	IFF	IFG	IMISCA	IAAC	ICARB	IFA	IFS	IPMCX	ICSAC	NOFE
Best	57.1	15.5	2.1	2.0	2.8	1.2	5.0	1.3	4.9	5.1	0	0	1.8	1.0	0.2
2nd	10.6	26.2	11.8	5.9	6.0	4.5	8.7	4.5	6.9	7.3	1.6	0	3.2	2.0	0.8
3rd	5.7	16.1	24.2	8.1	7.9	6.6	7.0	5.2	5.6	5.4	2.3	0	2.8	1.9	1.1
4th	4.4	11.9	25.1	9.4	8.2	8.4	6.7	6.1	4.8	4.7	3.3	0.1	3.1	2.3	1.6
5th	3.3	9.2	18.6	11.0	9.2	10.0	7.2	8.3	5.3	5.1	4.6	0.3	3.9	2.3	1.7
6th	3.1	7.2	10.8	11.8	10.1	11.3	7.9	9.7	5.7	5.6	5.9	1.5	3.9	3.0	2.7
7th	2.9	5.1	4.9	12.7	10.4	11.2	7.5	10.6	5.9	5.6	7.2	3.9	5.3	3.7	3.1
8th	2.4	3.5	1.9	11.1	9.9	10.4	7.8	10.5	6.7	5.9	8.4	8.5	5.1	4.1	3.8
9th	2.2	2.3	0.6	9.0	9.3	9.7	7.1	9.6	6.0	5.8	8.4	14.6	5.6	4.7	5.1
10th	1.4	1.4	0.1	7.5	7.5	8.3	6.6	8.7	6.9	5.8	8.6	20.0	6.3	5.2	5.7
11th	1.5	0.7	0	4.8	6.4	6.8	6.9	7.9	6.8	6.2	9.9	21.8	6.8	6.4	7.2
12th	1.3	0.6	0	3.5	5.4	5.6	7.3	6.5	7.6	7.0	10.4	17.4	9.1	8.5	9.7
13th	1.5	0.3	0	2.0	4.2	3.8	6.9	5.7	8.8	8.5	11.9	8.6	11.3	12.5	13.9
14th	1.3	0.1	0	1.0	2.2	1.9	5.3	3.6	9.8	10.1	10.9	2.9	14.4	16.5	19.9
Worst	1.2	0	0	0.3	0.6	0.4	2.2	1.6	8.4	11.8	6.4	0.4	17.4	25.9	23.4
MEAN RANK	**3·1**	**3.7**	**4·1**	**6·7**	**7·2**	**7.4**	**7·6**	**8·0**	**8.8**	**8·9**	**10·0**	**10·4**	**10·6**	**11·6**	**12·0**
SUCRA	**0·85**	**0·81**	**0·78**	**0·59**	**0·56**	**0·55**	**0·53**	**0·50**	**0.47**	**0·43**	**0·36**	**0·33**	**0·32**	**0·25**	**0·22**

Shaded values are probabilities above 5%
FASG, ferrous asparto glycinate; IAAC, iron amino acid chelate; ICARB, carbonyl iron; ICSAC, iron chondroitinsulfuric acid complex; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

b) Serum ferritin

Rank	IVISU	IMISCA	FASG	IFA	LAC	IPMCX	IAAC	IFS	IFF
Best	19.5	34.6	21.0	2.7	13.1	4.4	4.8	0	0
2nd	36.4	17.9	12.8	8.4	10.7	8.3	5.0	0.3	0.1
3rd	27.9	12.7	11.2	14.9	11.0	12.5	7.2	1.9	0.6
4th	12.4	10.6	12.8	20.1	11.7	15.1	8.7	7.3	1.4
5th	3.3	8.6	10.3	18.3	12.7	17.9	9.7	15.8	3.3
6th	0.4	6.0	7.9	14.3	11.4	15.7	11.5	26.6	6.2
7th	0.1	4.2	8.0	11.8	10.3	12.5	12.4	29.4	11.3
8th	0	3.7	8.8	7.3	10.7	10.0	19.0	16.2	24.4
Worst	0	1.7	7.3	2.1	8.4	3.6	21.6	2.5	52.7
MEAN RANK	**2·5**	**3·0**	**4·2**	**4·8**	**4·8**	**5·0**	**6.2**	**6·3**	**8·1**
SUCRA	**0·82**	**0·74**	**0·60**	**0·53**	**0·53**	**0·50**	**0.35**	**0·34**	**0·11**

Shaded values are probabilities above 5%
FASG, ferrous asparto glycinate; IAAC, iron amino acid chelate; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFS, ferrous sulphate; IPMCX, iron polymaltose complex; IMISCA, intramuscular iron sorbitol citric acid; IVISU, intravenous iron sucrose; LAC, lactoferrin

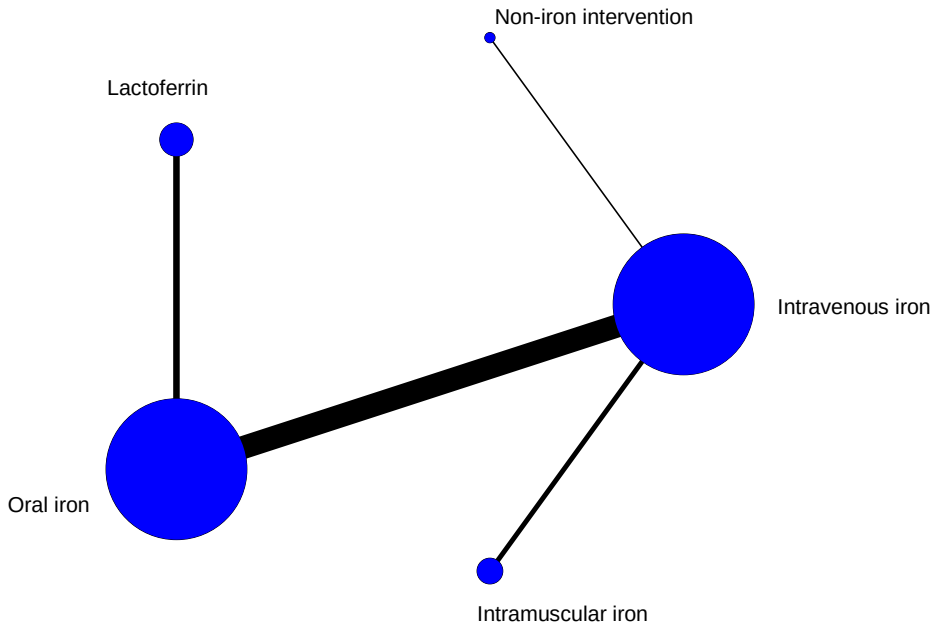
Appendix 8 Additional analyses

1. Secondary approach to intervention grouping

a) Route of administration – Haemoglobin (g/L)

(i) Network summary and map

	Haemoglobin
Number of studies	22
Number of women	2405
Number of unique interventions	5

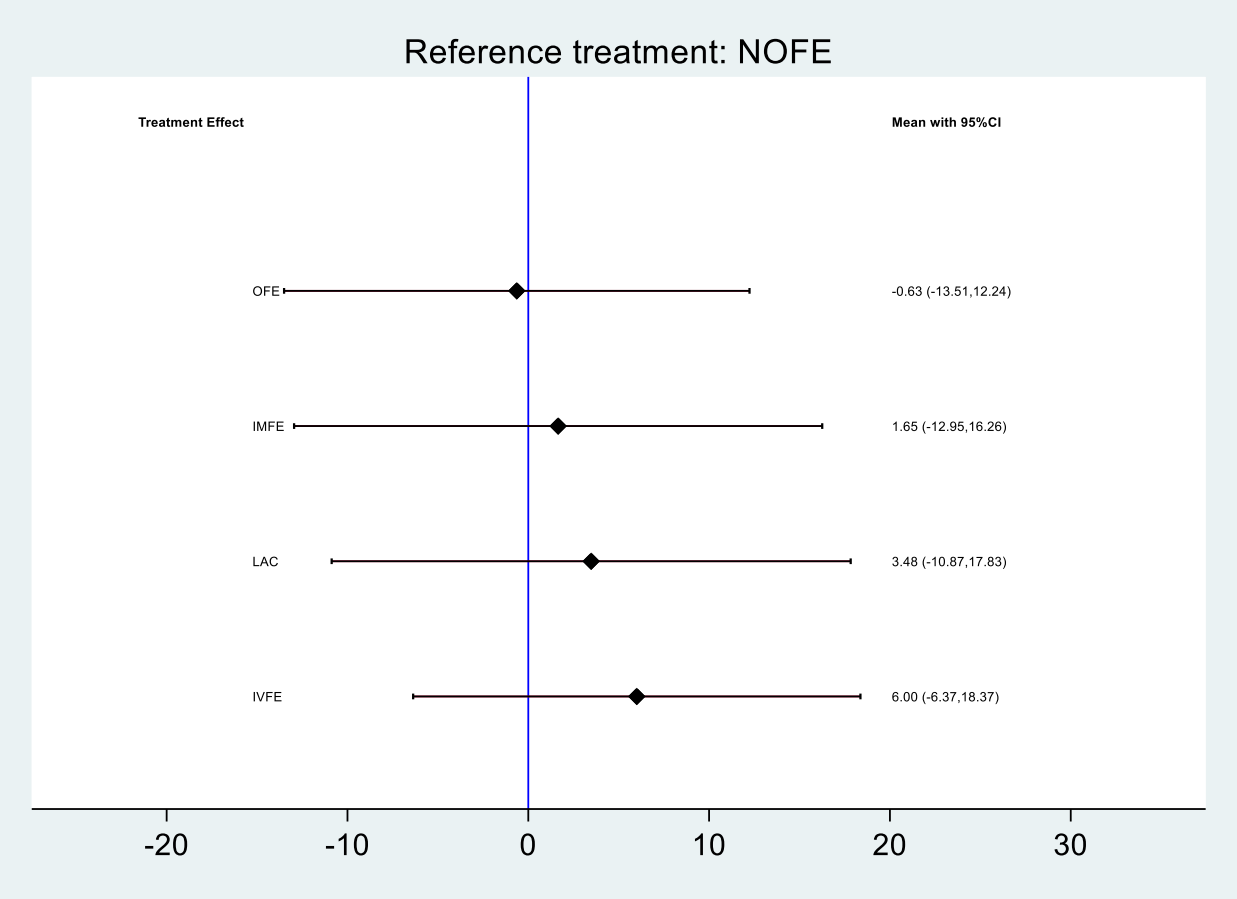


(ii) Network evidence for Haemoglobin from a consistency model assuming constant heterogeneity variance across all comparisons

Comparisons		Network evidence
Experimental	**Comparator**	**MD (95% CI)**
Intravenous iron	Intramuscular iron	4·3 (-4·0 to 12·1)
	Oral iron	6·6 (3·1 to 10·2)
	"Non-iron intervention"	6·0 (-6·4 to 18·4)
Lactoferrin	Oral iron	4·1 (-2·2 to 10·5)

Between study heterogeneity estimate (standard error): τ=6·3(1·2)

(iii) Interval plot with "Non-iron intervention" as the reference route of administration



LAC, lactoferrin; IVFE, intravenous iron; IMFE, Intramuscular iron; NOFE, "Non-iron intervention"; OFE, Oral iron

(iv) Ranking of routes of administration for haemoglobin

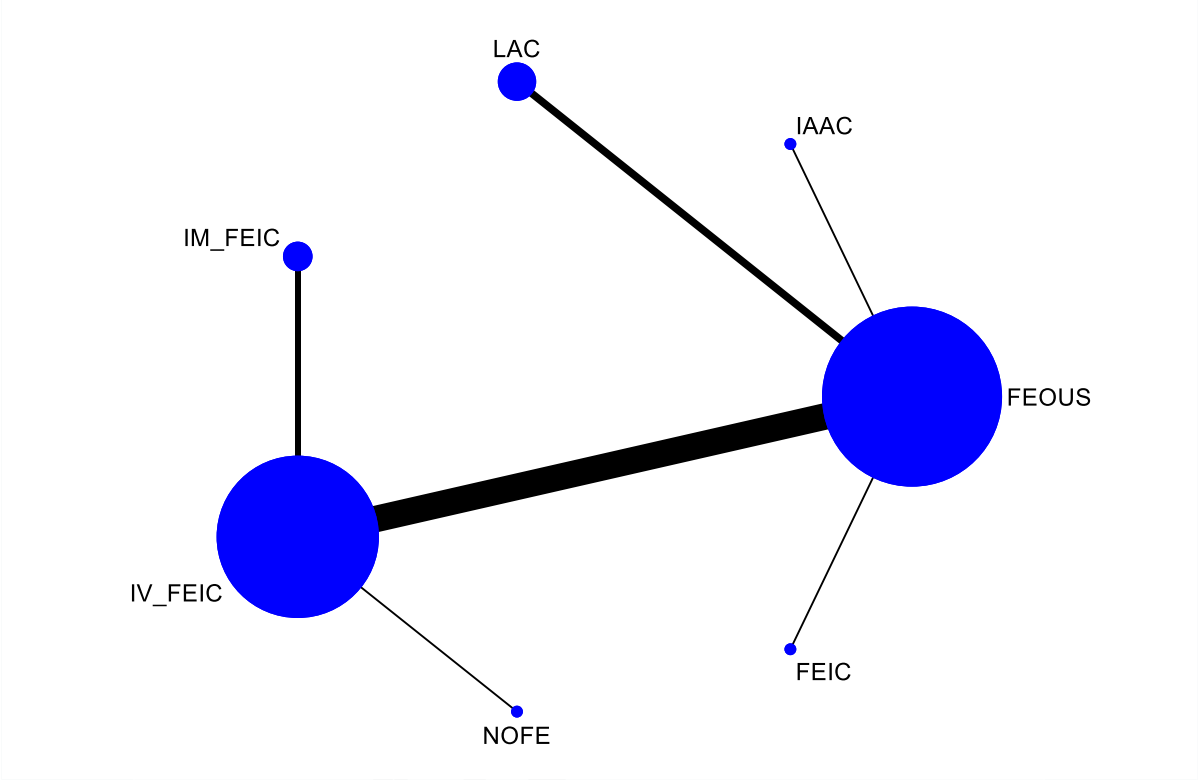
Rank	IVFE	LAC	IMFE	NOFE	OFE
Best	54.0	20.9	10.7	14.4	0
2nd	37.3	30.0	19.4	11.8	1.6
3rd	8.2	28.6	27.9	16.5	18.8
4th	0.5	15.2	23.8	15.7	44.9
Worst	0	5.4	18.3	41.7	34.7
MEAN RANK	**1.6**	**2.5**	**3.2**	**3.6**	**4.1**
SUCRA	**0.86**	**0.62**	**0.45**	**0.35**	**0.22**

Shaded values are probabilities above 5%
LAC, lactoferrin; IVFE, intravenous iron; IMFE, Intramuscular iron; NOFE, "Non-iron intervention"; OFE, Oral iron

b) Iron salt & route of administration – haemoglobin (g/L)

(i) Network summary and map

	Haemoglobin
Number of studies	24
Number of women	2533
Number of unique interventions	7



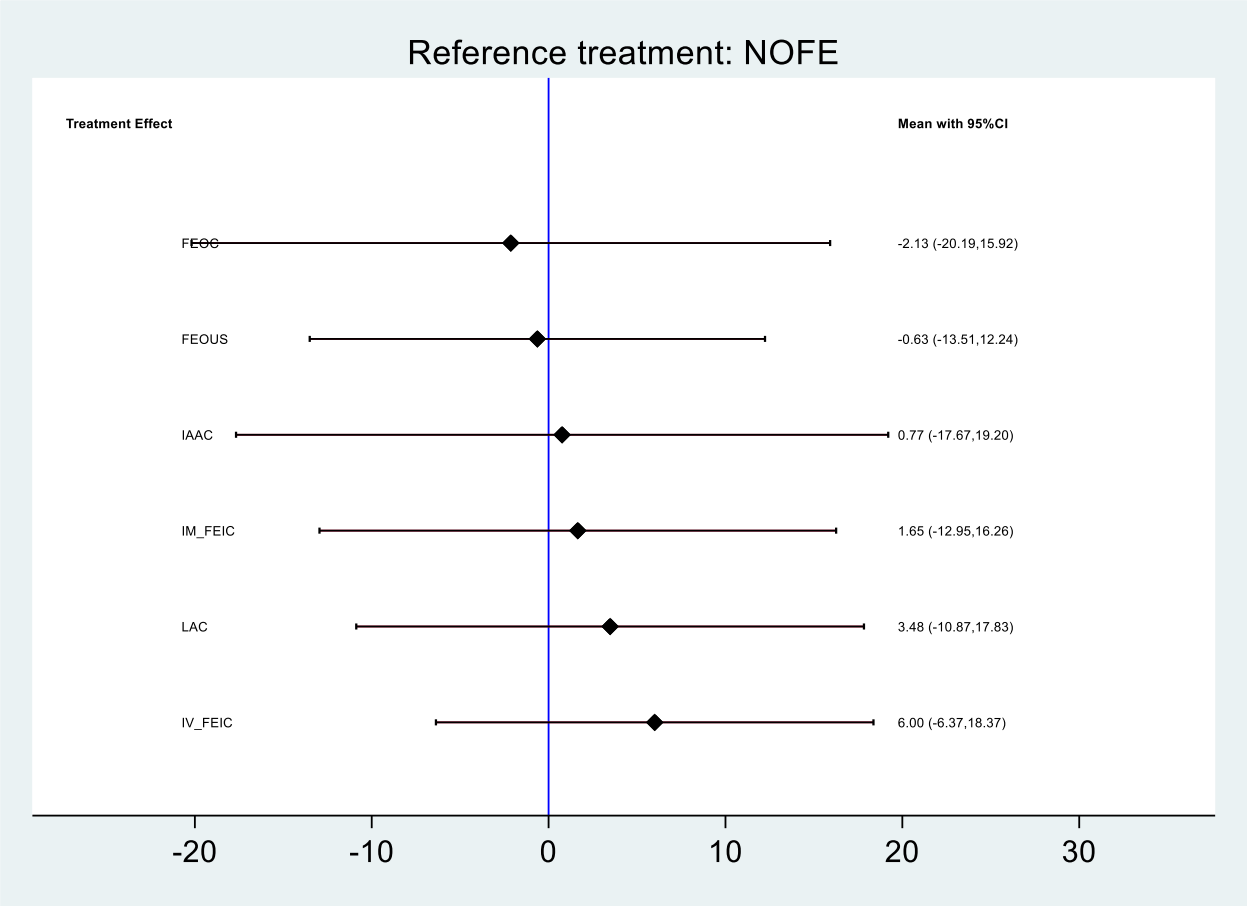
Unique interventions: LAC, Lactoferrin; IAAC, Iron amino acid chelate; IV_FEIC, Intravenous ferric salt; IM_FEIC, Intramuscular ferric salt; FEIC, Oral ferric salt; FEOUS, Oral ferrous salt; NOFE, "Non-iron intervention"

(ii) Network evidence for haemoglobin from a consistency model assuming constant heterogeneity variance across all comparisons

Comparisons		Network evidence
Experimental	**Comparator**	**MD (95% CI)**
Oral ferrous salt	Oral ferric salt	1·5 (-11·2 to 14·2)
	Iron amino acid chelate	-1·4 (14·6 to 11·8)
	Lactoferrin	-4·1 (-10·5 to 2·2)
	Intravenous ferric salt	-6·6 (-10·2 to -3·1)
Intravenous ferric salt	Intramuscular ferric salt	4·3 (-3·4 to 12·1)
	"Non-iron intervention"	6·0 (-6·4 to 18·4)

Between study heterogeneity estimate (standard error): τ=6·3(1·2)

(iii) Interval plot with "Non-iron intervention" as the reference iron salt and route of administration



Unique interventions: LAC, Lactoferrin; IAAC, Iron amino acid chelate; IV_FEIC, Intravenous ferric salt; IM_FEIC, Intramuscular ferric salt; FEIC, Oral ferric salt; FEOUS, Oral ferrous salt; NOFE, "Non-iron intervention"

(iv) Ranking of iron salt and route of administration for haemoglobin

Rank	IV_FEIC	LAC	IM_FEIC	IAAC	NOFE	FEOUS	FEIC
Best	37.2	16.5	8.1	18.2	12.8	0	7.2
2nd	39.4	21.3	13.2	9.7	9.5	0.3	6.6
3rd	18.3	24.6	19.3	11.7	12.5	5.0	8.6
4th	4.3	19.4	20.0	12.4	12.4	20.9	10.6
5th	0.7	10.6	16.6	11.8	11.6	36.8	11.8
6th	0	5.6	14.5	15.7	17.3	28.7	18.1
Worst	0	1.9	8.3	20.5	23.9	8.3	37.0
MEAN RANK	**1.9**	**3.1**	**4.0**	**4.2**	**4.5**	**5.1**	**5.2**
SUCRA	**0.85**	**0.65**	**0.50**	**0.47**	**0.42**	**0.31**	**0.31**

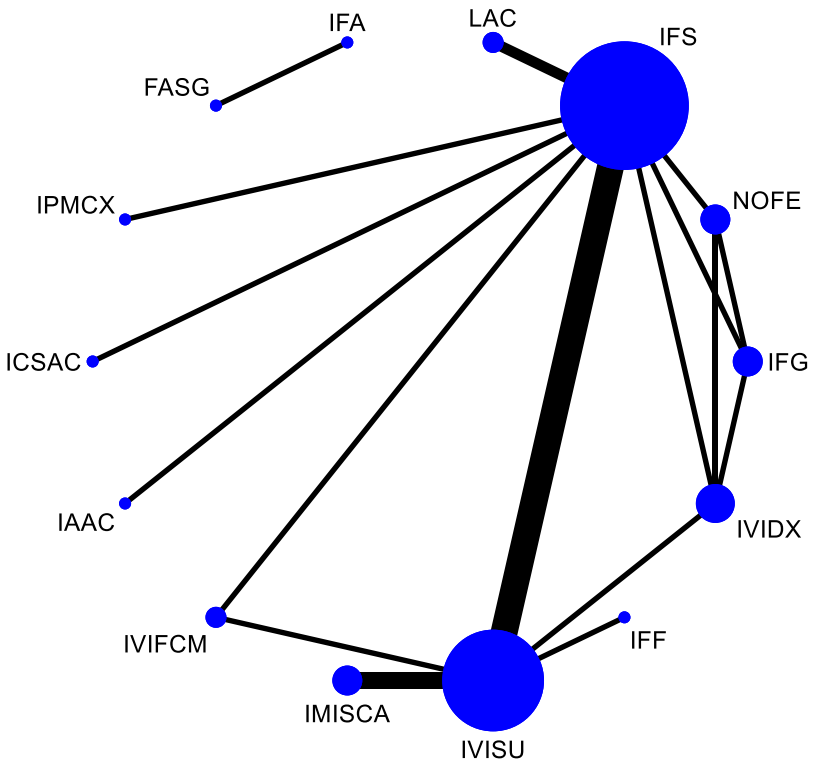
Shaded values are probabilities above 5%
LAC, Lactoferrin; IAAC, Iron amino acid chelate; IV_FEIC, Intravenous ferric salt; IM_FEIC, Intramuscular ferric salt; FEIC, Oral ferric salt; FEOUS, Oral ferrous salt; NOFE, "Non-iron intervention"

2. Sensitivity analyses

a) Interventions without vitamins – haemoglobin (g/L)

(i) Network summary and map

	Haemoglobin
Number of studies	20
Number of women	1989
Number of unique interventions	14



Unique interventions: FASG, ferrous asparto glycinate; IAAC, iron amino acid chelate; ICSAC, iron chondroitinsulfuric acid complex; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

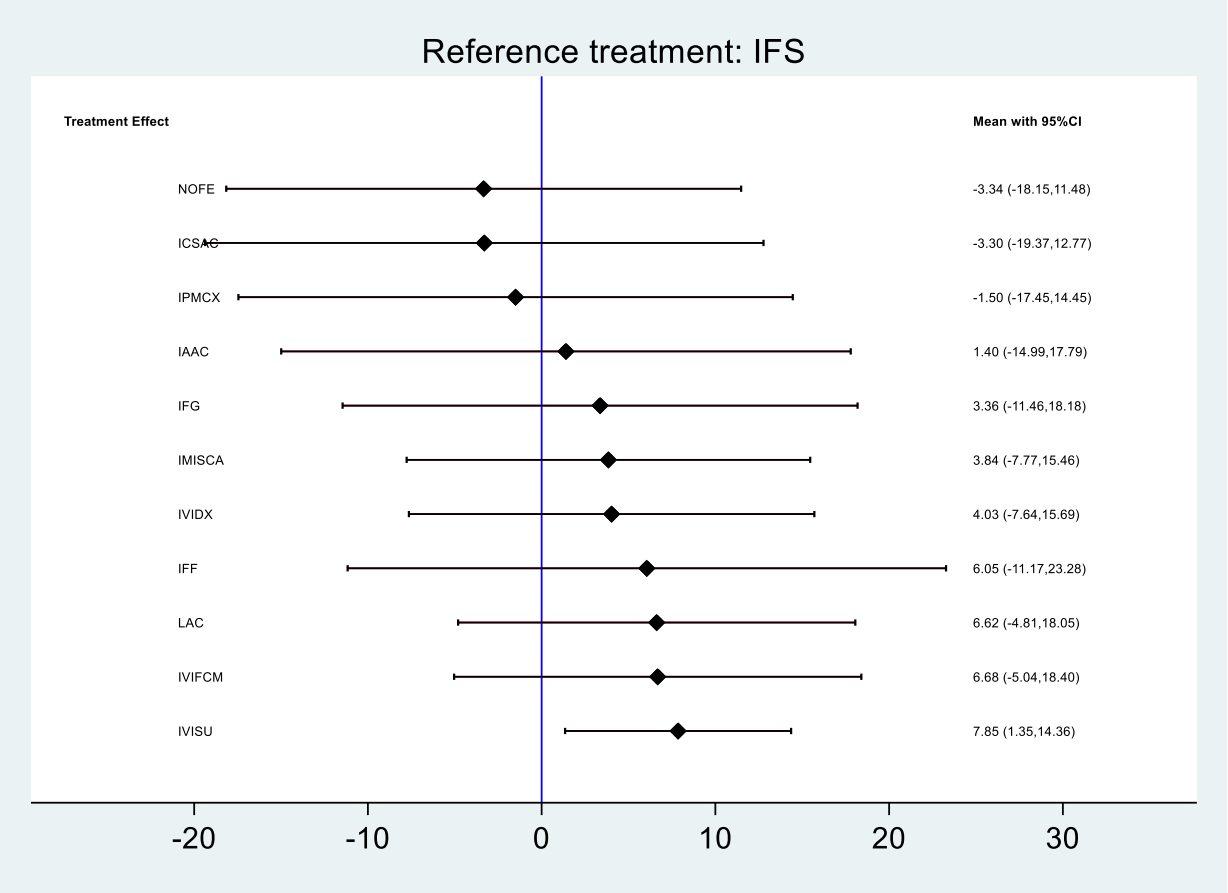
NB disconnected network, so following analyses do not contain the FASG-IFA comparison (Kamdi 2015). Therefore, only 12 unique interventions are included in the connected network.

(ii) Network evidence for haemoglobin from a consistency model assuming constant heterogeneity variance across all comparisons

Comparisons		Network evidence MD (95% CI)
Experimental	**Comparator**	
Ferrous fumarate	Iron sucrose (IV)	-1·8 (-17·7 to 14·1)
Ferrous gluconate	Iron dextran (IV)	-0·7 (-15·5 to 14·2)
	"Non-iron intervention"	6·7 (-9·0 to 22·4)
Ferrous sulphate	Iron amino acid chelate	-1·4 (-17·8 to 15·0)
	Ferrous gluconate	-3·4 (-18·2 to 11·5)
	Iron chondroitin sulphuric acid	3·3 (-12·8 to 19·4)
	Iron polymaltose complex	1·5 (-14·5 to 17·5)
	Iron dextran (IV)	-4·0 (-15·7 to 7·6)
	Ferric carboxymaltose (IV)	-6·7 (-18·4 to 5·0)
	Iron sucrose (IV)	-7·9 (-14·4 to -1·3)
	Lactoferrin	-6·6 (-18·1 to 4·8)
	"Non-iron intervention"	3·3 (-11·5 to 18·2)
Iron dextran (IV)	"Non-iron intervention"	7·4 (-7·5 to 22·2)
Iron sucrose (IV)	Iron dextran (IV)	3·8 (-7·9 to 15·5)
	Ferric carboxymaltose (IV)	1·2 (-10·5 to 12·9)
Iron sorbitol citric acid (IM)	Iron sucrose (IV)	-4·0 (-13·6 to 5·6)

Between study heterogeneity estimate (standard error): τ=8·0(2·0)

(iii) Interval plot with ferrous sulphate as the reference intervention



IAAC, iron amino acid chelate; ICSAC, Iron chondroitinsulfuric acid complex; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, Lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

(iv) Ranking of interventions without vitamins for Haemoglobin

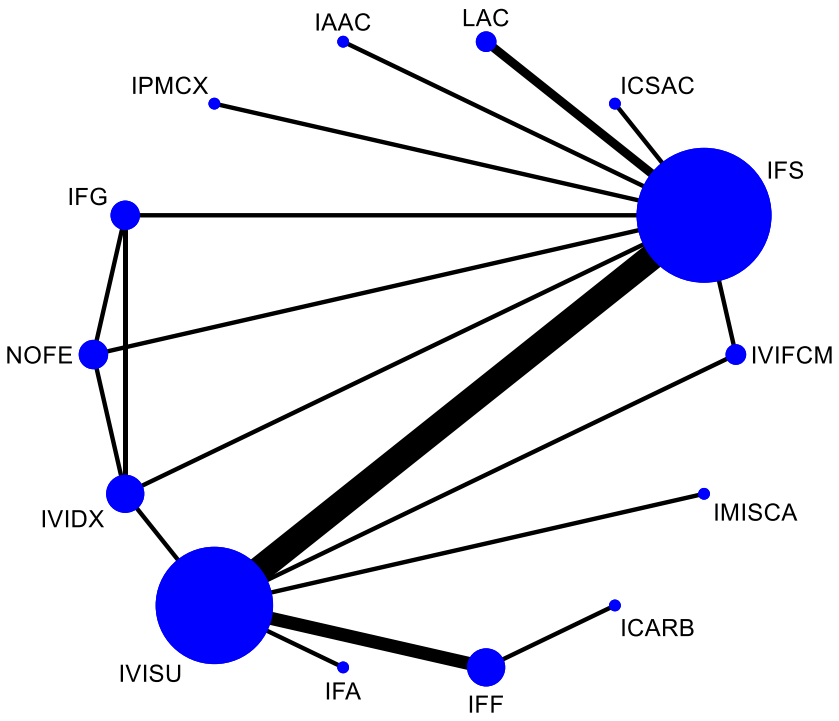
Rank	IVISU	LAC	IVIFCM	IFF	IVIDX	IMISCA	IFG	IAAC	IPMCX	IFS	ICSAC	NOFE
Best	7.5	16.3	15.8	21.1	5.9	5.7	10.5	9.1	4.4	0.0	2.6	1.3
2nd	19.8	14.2	13.9	11.1	8.4	7.6	9.0	6.9	4.0	0.0	3.1	2.0
3rd	25.1	11.5	12.5	8.8	9.7	8.9	7.5	6.0	4.3	0.2	3.4	2.2
4th	21.7	10.8	11.5	8.5	10.6	10.9	7.5	6.1	4.9	0.9	3.6	3.0
5th	14.2	10.7	11.2	7.6	11.8	11.6	8.6	7.0	5.6	3.2	4.7	3.8
6th	7.2	9.7	9.7	7.4	12.6	12.2	9.2	7.4	5.7	8.4	5.2	5.3
7th	3.1	8.2	7.5	7.0	11.3	10.8	9.3	7.8	6.8	16.5	5.5	6.2
8th	1.1	6.7	5.7	5.8	9.7	9.3	8.6	7.5	7.5	23.7	6.6	7.7
9th	0.3	4.8	4.8	5.9	8.0	8.4	8.7	8.5	8.6	24.0	8.6	9.5
10th	0.1	3.5	3.8	6.3	6.5	6.5	8.7	10.1	12.4	15.9	11.8	14.4
11th	0.0	2.4	2.6	5.7	4.3	5.3	8.2	11.9	15.8	6.2	17.7	20.0
Worst	0.0	1.2	1.1	5.0	1.3	2.6	4.2	11.7	20.1	1.0	27.4	24.5
MEAN RANK	**3.6**	**4.6**	**4.6**	**5.2**	**5.9**	**6.0**	**6.2**	**7.1**	**8.3**	**8.3**	**9.0**	**9.2**
SUCRA	**0.77**	**0.67**	**0.67**	**0.62**	**0.56**	**0.54**	**0.53**	**0.45**	**0.34**	**0.34**	**0.28**	**0.25**

Shaded values are probabilities above 5%
IAAC, iron amino acid chelate; ICSAC, Iron chondroitinsulfuric acid complex; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, Lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

(b) Study at low and medium risk of bias – Haemoglobin (g/L)

(i) Network summary and map

	Haemoglobin
Number of studies	21
Number of women	2207
Number of unique interventions	14



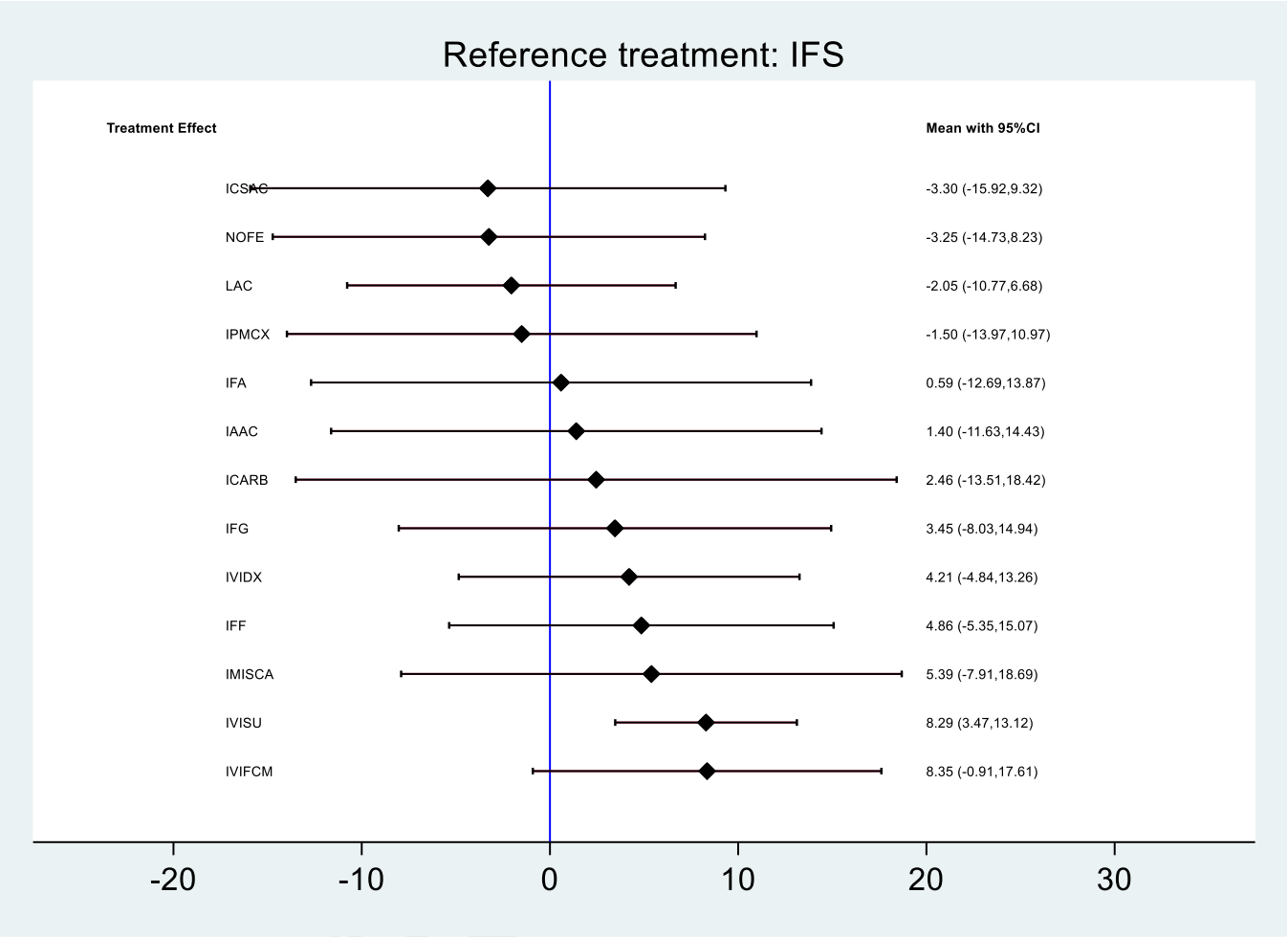
Unique interventions: IAAC, iron amino acid chelate; ICARB, carbonyl iron; ICSAC, iron chondroitinsulfuric acid complex; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

(ii) Network evidence for Haemoglobin from a consistency model assuming constant heterogeneity variance across all comparisons

Comparisons		Network evidence MD (95% CI)
Experimental	**Comparator**	
Ferrous ascorbate	Iron sucrose (IV)	-7·7 (-20·1 to 4·7)
Ferrous fumarate	Carbonyl iron	2·4 (-9·9 to 14·7)
	Iron sucrose (IV)	-3·4 (-12·4 to 5·6)
Ferrous gluconate	Iron dextran (IV)	-0·8 (-12·2 to 10·7)
	"Non-iron intervention"	6·7 (-5·5 to 18·9)
Ferrous sulphate	Iron amino acid chelate	-1·4 (-14·4 to 11·6)
	Ferrous gluconate	-3·5 (-14·9 to 8·0)
	Iron chondroitin sulphuric acid	3·3 (-9·3 to 15·9)
	Iron polymaltose complex	1·5 (-11·0 to 14·0)
	Iron dextran (IV)	-4·2 (-13·3 to 4·8)
	Ferric carboxymaltose (IV)	-8·3 (-17·6 to 0·9)
	Iron sucrose (IV)	-8·3 (-13·1 to -3·5)
	Lactoferrin	2·0 (-6·7 to 10·8)
	"Non-iron intervention"	3·2 (-8·2 to 14·7)
Iron dextran (IV)	"Non-iron intervention"	7·5 (-4·0 to 18·9)
Iron sucrose (IV)	Iron dextran (IV)	4·1 (-5·0 to 13·2)
	Ferric carboxymaltose (IV)	-0·1 (-9·3 to 9·2)
Iron sorbitol citric acid (IM)	Iron sucrose (IV)	-2·9 (-15·3 to 9·5)

Between study heterogeneity estimate (standard error): τ=6·2(1·6)

(iii) Interval plot with ferrous sulphate as the reference intervention



Shaded values are probabilities above 5%
IAAC, iron amino acid chelate; ICARB, carbonyl iron; ICSAC, iron chondroitinsulfuric acid complex; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

(iv) Ranking of interventions from low and medium risk of bias studies for Haemoglobin

Rank	IVISU	IVIFCM	IMISCA	IFF	IVIDX	IFG	ICARB	IAAC	IFA	IFS	IPMCX	ICSAC	LAC	NOFE
Best	10.5	27.3	17.3	6.0	4.9	8.1	10.6	6.6	4.2	0.0	2.3	1.4	0.3	0.5
2nd	25.3	18.0	10.1	9.2	6.8	7.7	7.0	5.8	4.1	0.0	2.7	1.7	0.6	0.8
3rd	28.6	12.4	9.4	10.9	9.0	6.8	5.9	5.0	4.3	0.1	3.0	2.0	1.3	1.3
4th	19.9	11.5	8.7	12.9	10.7	8.1	6.5	6.5	4.9	0.4	3.4	2.1	2.3	2.1
5th	10.0	9.6	8.8	12.8	12.5	9.4	7.7	6.8	6.7	1.4	4.5	3.6	3.5	2.8
6th	4.0	7.5	8.5	11.6	13.3	10.0	7.5	7.5	7.9	4.7	5.7	3.9	4.4	3.6
7th	1.1	4.9	7.5	9.9	12.0	9.8	6.5	7.4	8.0	10.5	6.6	4.7	6.0	5.2
8th	0.4	3.2	6.1	7.8	9.7	8.4	6.4	7.2	7.9	16.7	7.1	5.8	7.2	6.0
9th	0.1	2.4	4.9	6.3	7.3	7.3	6.1	6.9	7.0	22.6	7.1	6.4	8.7	7.2
10th	0.0	1.3	5.1	4.8	5.7	6.6	6.3	7.3	7.5	21.7	8.1	6.9	10.3	8.4
11th	0.0	1.0	4.2	3.8	4.3	6.6	6.4	8.3	8.6	13.8	9.6	9.4	13.3	10.7
12th	0.0	0.6	4.2	2.5	2.5	5.3	7.1	8.4	9.8	6.2	11.4	12.1	16.1	13.9
13th	0.0	0.3	3.2	1.3	1.1	4.2	7.7	8.7	9.7	1.7	13.2	16.2	15.2	17.6
Worst	0.0	0.1	2.0	0.3	0.3	1.6	8.3	7.8	9.3	0.2	15.4	23.8	10.9	19.9
MEAN RANK	3.1	3.6	5.6	5.7	6.1	6.6	7.4	8.0	8.5	9.2	9.6	10.6	10.3	10.7
SUCRA	0.84	0.80	0.65	0.64	0.61	0.57	0.51	0.47	0.42	0.37	0.34	0.26	0.29	0.25

Shaded values are probabilities above 5%

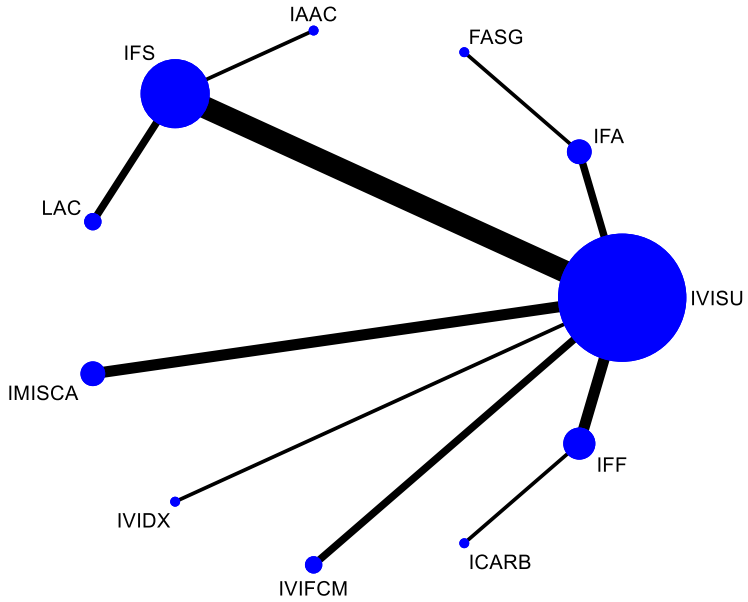
IAAC, iron amino acid chelate; ICARB, carbonyl iron; ICSAC, iron chondroitinsulfuric acid complex; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

3. Subgroup analysis by country income group

a) Low and middle income countries – Haemoglobin (g/L)

(i) Network summary and map

	Haemoglobin
Number of studies	22
Number of women	2541
Number of unique interventions	11



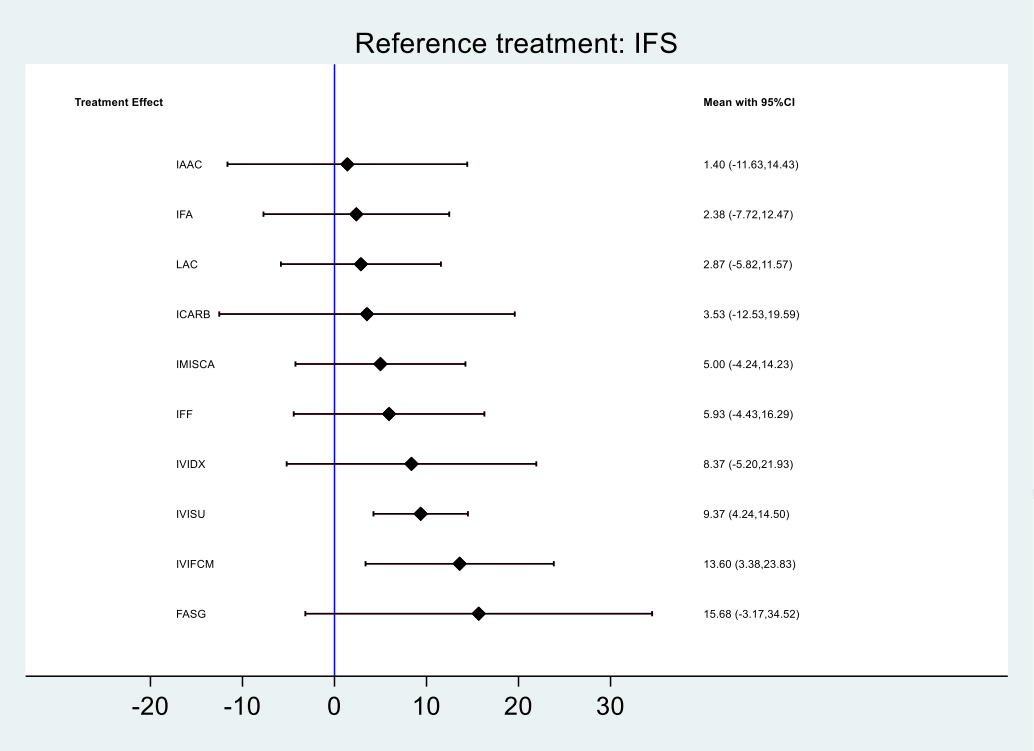
Unique interventions: FASG, ferrous asparto glycinate; IAAC, iron amino acid chelate; ICARB, carbonyl iron; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin;

(ii) Network evidence for Haemoglobin from a consistency model assuming constant heterogeneity variance across all comparisons

Comparisons		Network evidence
Experimental	**Comparator**	**MD (95% CI)**
Ferrous aspartic glycinate	Ferrous ascorbate	13·3 (-2·6 to 29·2)
Ferrous ascorbate	Iron sucrose (IV)	-7·0 (-15·7 to 1·7)
Ferrous fumarate	Carbonyl iron	2·4 (-9·9 to 14·7)
	Iron sucrose (IV)	-3·4 (-12·4 to 5·6)
Ferrous sulphate	Iron amino acid chelate	-1·4 (-14·4 to 11·6)
	Iron sucrose (IV)	-9·4 (-14·5 to -4·2)
	Lactoferrin	-2·9 (-11·6 to 5·8)
Iron sucrose (IV)	Iron dextran (IV)	1·0 (-11·6 to 13·6)
	Ferric carboxymaltose (IV)	-4·2 (-13·1 to 4·6)
Iron sorbitol citric acid (IM)	Iron sucrose (IV)	-4·4 (-12·0 to 3·3)

Between study heterogeneity estimate (standard error): τ=6·2(1·4)

(iii) Interval plot with ferrous sulphate as the reference intervention



Unique interventions: FASG, ferrous asparto glycinate; IAAC, iron amino acid chelate; ICARB, carbonyl iron; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin;

(iv) Ranking of interventions from studies from low and middle income countries for Haemoglobin

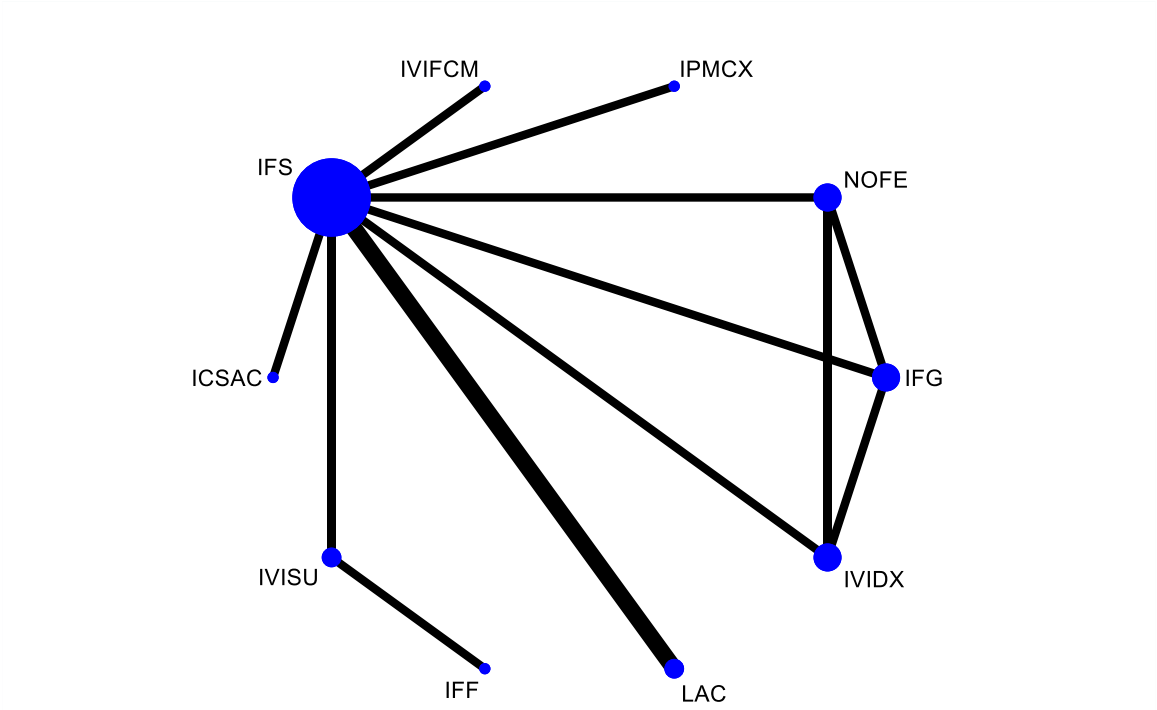
Rank	IVIFCM	FASG	IVISU	IVIDX	IFF	IMISCA	ICARB	LAC	IFA	IAAC	IFS
Best	29.1	50.6	1.2	10.0	1.6	0.9	4.1	0.7	0.1	1.7	0.0
2nd	35.5	16.6	9.8	15.6	5.6	2.9	6.8	2.5	0.9	3.8	0.0
3rd	15.8	7.8	28.3	14.6	9.3	6.0	6.9	4.2	2.4	4.7	0.0
4th	7.7	5.4	32.5	10.5	11.8	9.7	6.7	5.6	4.7	5.2	0.1
5th	5.0	4.8	19.0	10.2	15.6	14.4	7.9	8.7	7.8	5.9	0.8
6th	3.5	4.0	7.4	9.6	16.7	15.8	9.0	11.6	11.7	8.2	2.6
7th	2.0	3.3	1.6	8.3	14.3	16.5	9.8	13.2	14.6	9.3	7.2
8th	0.8	2.3	0.3	6.8	10.5	13.8	9.5	14.6	15.7	10.0	15.7
9th	0.3	1.8	0.0	5.6	7.3	9.3	8.7	14.3	14.1	11.9	26.7
	0.1	1.8	0.0	4.4	5.5	6.9	11.1	13.4	14.3	12.5	30.1
Worst	0.1	1.7	0.0	4.3	1.8	4.0	19.6	11.2	13.7	26.9	16.9
MEAN RANK	**2.5**	**2.7**	**3.9**	**4.9**	**5.9**	**6.5**	**7.1**	**7.5**	**7.9**	**8.0**	**9.2**
SUCRA	**0.85**	**0.83**	**0.71**	**0.61**	**0.51**	**0.45**	**0.39**	**0.35**	**0.31**	**0.31**	**0.18**

Shaded values are probabilities above 5%
FASG, ferrous asparto glycinate; ICARB, carbonyl iron; IFA, ferrous ascorbate; IFF, ferrous fumarate; IFS, ferrous sulphate; IMISCA, intramuscular iron sorbitol citric acid; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin

(b) High income countries – Haemoglobin (g/L)

(i) Network summary and map

	Haemoglobin
Number of studies	8
Number of women	702
Number of unique interventions	10



Unique interventions: ICSAC, iron chondroitinsulfuric acid complex; IFF, ferrous fumarate; IFG, ferrous gluconate; IFS, ferrous sulphate; IPMCX, iron polymaltose complex; IVIDX, intravenous iron dextran; IVIFCM, intravenous ferric carboxymaltose; IVISU, intravenous iron sucrose; LAC, lactoferrin; NOFE, "Non-iron intervention" (placebo/vitamin/no intervention)

(ii) Network evidence for Haemoglobin from a consistency model assuming constant heterogeneity variance across all comparisons

Between study heterogeneity estimate (standard error): τ=12·5(9·1)
Due to considerable heterogeneity and lack of data, further results are not presented

Appendix 9 Adverse events

Iron preparation	Group	Adverse Event	Event	Sample	*Study*
FASG	**GI**	GI upset	1	26	*Kamdi 2015*
ICARB	**GI**	Abdominal pain	3	75	*Sagaonkar 2009*
		Constipation	38	110	*Sagaonkar 2009*
		Diarrhoea	5	77	*Sagaonkar 2009*
		Nausea	33	105	*Sagaonkar 2009*
		Vomiting	2	74	*Sagaonkar 2009*
IAAC	**GI**	Nausea	11	24	*Santiago 2019*
		Vomiting	9	24	*Santiago 2019*
		Constipation	7	24	*Santiago 2019*
		Dark Stool	16	24	*Santiago 2019*
		Epigastric Pain	2	24	*Santiago 2019*
IFA	**General**	Fever	NR	100	*Rudra 2016*
		Hot flush	0	100	*Deeba 2012*
		Itch (entire body)	NR	100	*Rudra 2016*
		Metallic taste	0	100	*Deeba 2012*
			4	100	*Rudra 2016*
	GI	Diarrhoea	5	100	Deeba 2012
			4	100	Rudra 2016
		Epigastric discomfort and bloating	16	100	Rudra 2016
		GI upset*	3	24	Kamdi 2015
		Nausea	0	100	Deeba 2012
			NR	100	Rudra 2016
		Upper GI upset*	22	100	Deeba 2012
		Vomiting	4	100	Rudra 2016
	Local/reaction	Injection site swelling/redness/pain	NR	100	Rudra 2016
	Muscular	Arthralgia	0	100	Deeba 2012
			NR	100	Rudra 2016
	Nervous System	Dizziness	0	100	Deeba 2012
	Other	Serious Adverse Events	NR	100	Rudra 2016
IFF	**GI**	Abdominal discomfort	13	33	*Darwish 2017*
		Abdominal pain	0	72	*Sagaonkar 2009*
		Constipation	20	33	*Darwish 2017*
			18	90	*Sagaonkar 2009*
		Diarrhoea	2	56	*Bhavi 2017*
			1	73	*Sagaonkar 2009*
		Gastritis	4	56	*Bhavi 2017*
		Nausea and/or vomiting	11	33	*Darwish 2017*
			14	86	*Sagaonkar 2009*
			8	56	*Bhavi 2017*
			13	33	*Darwish 2017*
			0	72	*Sagaonkar 2009*
			2	100	*Sharma 2004*
	Local/discoloration	Skin staining at injection site	0	100	*Sharma 2004*
	Local/pain	Burning/pain at the site of injection	0	56	*Bhavi 2017*
		Injection site reaction/inflammation/swelling	0	33	*Darwish 2017*
	Muscular	Arthralgia	0	100	*Sharma 2004*
	Other/Combined	Side effects	10	44	*Neeru 2012*
		Serious Adverse Events	0	40	*NCT00746551*
	Systemic	Allergic reaction	0	33	*Darwish 2017*
		Systemic reaction	0	100	*Sharma 2004*
IFG	**GI**	Abdominal cramps	2	24	*Symonds 1969*
		Constipation	4	24	*Symonds 1969*

		Nausea and vomiting	4	24	*Symonds 1969*
	Other	Other symptoms	3	24	*Symonds 1969*
IFS	**Cardiac**	Change in blood pressure	0	25	*Aggarwal 2012*
		Bradycardia	NR	NR	*Neogi 2019*
		Tachycardia	0	75	*Arzoo 2020*
		Hypertension	NR	NR	*Neogi 2019*
		Syncope	1	124	*Breymann 2016*
			NR	NR	*Neogi 2019*
		Vasovagal due to apprehension	0	75	*Kumar 2005*
	General	Altered Taste	3	25	*Aggarwal 2012*
		Bronchospasm	0	124	*Breymann 2016*
			1	39	*Ortiz 2011*
		Chest compression	NR	NR	*Neogi 2019*
		Dysgeusia	0	124	*Breymann 2016*
		Fever	0	25	*Aggarwal 2012*
			1	50	*Gupta 2014*
			0	75	*Kumar 2005*
			0	75	*Mehta 2014*
			0	100	*Sharma 2004*
		immediate AE	NR	NR	*Neogi 2019*
		late AE	NR	NR	*Neogi 2019*
			0	59	*AlMomen 1996*
		Itching all over body	1	50	*Gupta 2014*
		Itching and rash	0	75	*Kumar 2005*
		Malaise	*0*	*75*	*Kumar 2005*
			0	*100*	*Sharma 2004*
		Metallic taste	5	50	*Abhilashini 2014*
			0	50	*Gupta 2014*
			6	75	*Mehta 2014*
			1	75	*Dalal 2018*
		immediate AE	NR	NR	*Neogi 2019*
		late AE	NR	NR	*Neogi 2019*
		Pruritus	0	50	*Abhilashini 2014*
			1	39	*Ortiz 2011*
		Rash	1	124	*Breymann 2016*
		Rash and itching	1	100	*Sharma 2004*
		Rashes or pruritus	NR	NR	*Neogi 2019*
		Tightness and discomfort in the skin	0	59	*AlMomen 1996*
		Urticarial reactions	0	98	*Khalafallah 2010*
	General/Pain	Severe systemic ache and arthralgia	0	100	*Sharma 2004*
	General/Systemic	Vasovagal attack	0	100	*Sharma 2004*
	GI	Abdominal cramps	1	25	*Symonds 1969*
		Abdominal pain	5	124	*Breymann 2016*
			1	39	*Ortiz 2011*
			60	100	*Rezk 2016*
			10	75	*Arzoo 2020*
			12	50	*Gawai 2020*
		Constipation	1	50	*Abhilashini 2014*
			2	25	*Aggarwal 2012*
			3	124	*Breymann 2016*
			0	50	*Gupta 2014*
			4	50	*Kochhar 2013*
			8	75	*Kumar 2005*
			3	48	*Nappi 2009*
			NR	NR	*Neogi 2019*
			9	39	*Ortiz 2011*
			60	100	*Rezk 2016*

			5	100	*Sharma 2004*
GI	Constipation		1	25	*Symonds 1969*
			1	75	*Dalal 2018*
			11	24	*Santiago 2019*
			46	50	*Gawai 2020*
	Constipation or Diarrhea		13	75	*Mehta 2014*
	Dark stools		17	24	*Santiago 2019*
			45	50	*Gawai 2020*
	Diarrhoea		2	50	*Abhilashini 2014*
			5	25	*Aggarwal 2012*
			1	23	*Bayoumeu 2002*
			4	124	*Breymann 2016*
			0	50	*Gupta 2014*
			2	50	*Kochhar 2013*
			5	75	*Kumar 2005*
			0	48	*Nappi 2009*
			2	39	*Ortiz 2011*
			3	100	*Sharma 2004*
			NR	NR	*Neogi 2019*
			2	75	*Dalal 2018*
	Dyspepsia		6	50	*Abhilashini 2014*
			3	124	*Breymann 2016*
			9	75	*Kumar 2005*
			10	100	*Sharma 2004*
			5	75	*Dalal 2018*
	Epigastric pain		0	39	*Ortiz 2011*
			2	48	*Nappi 2009*
			3	24	*Santiago 2019*
	Epigastric discomfort		0	50	*Gupta 2014*
	Epigastric discomfort /Nausea/ Vomiting		16	75	*Mehta 2014*
	Gastritis		3	25	*Aggarwal 2012*
			NR	NR	*Neogi 2019*
	GI upset		18	59	*AlMomen 1996*
			16	124	*Breymann 2016*
		mild	27	98	*Khalafallah 2010*
			60	100	*Rezk 2016*
			42	50	*Gawai 2020*
	Heartburn		2	50	*Kochhar 2013*
			11	75	*Arzoo 2020*
	Hiccup		0	50	*Kochhar 2013*
	Nausea and/or vomiting		NR	NR	*Neogi 2019*
		Nausea	2	25	*Aggarwal 2012*
			4	50	*Abhilashini 2014*
			2	25	*Aggarwal 2012*
			6	124	*Breymann 2016*
			3	50	*Kochhar 2013*
			NR	30	*Komolafe 2003*
			18	39	*Ortiz 2011*
			18	24	*Santiago 2019*
		Vomiting	3	50	*Abhilashini 2014*
			2	124	*Breymann 2016*
			2	75	*Kumar 2005*
			1	48	*Nappi 2009*
			11	39	*Ortiz 2011*
			30	100	*Rezk 2016*
			2	75	*Dalal 2018*
GI			17	24	*Santiago 2019*

			31	50	*Gawai 2020*
		Nausea and vomiting	0	50	*Gupta 2014*
			4	25	*Symonds 1969*
			12	75	*Arzoo 2020*
	Local/discoloration	Skin staining	0	100	*Sharma 2004*
			NR	30	*Komolafe 2003*
			0	75	*Kumar 2005*
	Local/pain	Local pain	0	75	*Kumar 2005*
		Mild	0	100	*Sharma 2004*
		Severe	0	100	*Sharma 2004*
		Pain at the site of injection	0	75	*Mehta 2014*
			1	50	*Gupta 2014*
		Mild	NR	30	*Komolafe 2003*
		Significant	NR	30	*Komolafe 2003*
	Muscular	Arthralgia	0	75	*Kumar 2005*
			NR	NR	*Neogi 2019*
		Myalgia	0	50	*Abhilashini 2014*
			NR	NR	*Neogi 2019*
	Nervous System	Dizziness	0	124	*Breymann 2016*
		Headache	0	25	*Aggarwal 2012*
			1	124	*Breymann 2016*
			1	50	*Kochhar 2013*
			NR	30	*Komolafe 2003*
			NR	NR	*Neogi 2019*
			2	39	*Ortiz 2011*
		Headache and giddiness	0	100	*Sharma 2004*
		Immediate headache and giddiness	0	75	*Kumar 2005*
		Nervous system disorders	1	124	*Breymann 2016*
	Other	Could not tolerate drug	4	59	*AlMomen 1996*
		General disorders & administration-site conditions	0	124	*Breymann 2016*
		Change in taste	0	23	*Bayoumeu 2002*
		Other symptoms	3	25	*Symonds 1969*
		Side effects	16	75	*Kumar 2005*
		Unable to tolerate the drug	7	98	*Khalafallah 2010*
		Want to stop intake	20	100	*Rezk 2016*
	Pain	Arthritis	0	25	*Aggarwal 2012*
		Back pain	1	39	*Ortiz 2011*
	Systemic	Anaphylaxis Grade 1	0	25	*Aggarwal 2012*
		Anaphylaxis Grade 2	0	25	*Aggarwal 2012*
		Anaphylactic reaction	NR	NR	*Neogi 2019*
		Allergic reaction	1	75	*Arzoo 2020*
		Systemic ache	0	75	*Kumar 2005*
			0	100	*Sharma 2004*
	Vascular	Thrombophlebitis	0	25	*Aggarwal 2012*
			NR	NR	*Neogi 2019*
			2	50	*Gupta 2014*
		Phlebitis	0	75	*Mehta 2014*
		Vascular disorders	0	124	*Breymann 2016*
IMISCA	**Cardiac**	Tachycardia	3	65	*Nanthini 2017*
		Vasovagal due to apprehension	1	75	*Kumar 2005*
	General	Fever	4	75	*Kumar 2005*
			4	65	*Nanthini 2017*
		Itching and rash	8	73	*Kumar 2005*
		Malaise	2	75	*Kumar 2005*
	GI	Abdominal pain	0	50	*Singh 2012*
		Constipation	0	75	*Kumar 2005*

		Diarrhoea	0	75	*Kumar 2005*
		Dyspepsia	0	75	*Kumar 2005*
		Gastritis	2	30	*Dhanani 2012*
		Nausea and vomiting	8	65	*Nanthini 2017*
			2	30	*Dhanani 2012*
		Vomiting	0	75	*Kumar 2005*
	Local	Itching at injection site	0	65	*Nanthini 2017*
		Swelling	15	65	*Nanthini 2017*
			5	30	*Dhanani 2012*
	Local/discoloration	Skin staining	7	30	*Dhanani 2012*
			5	50	*Singh 2012*
			26	75	*Kumar 2005*
			13	65	*Nanthini 2017*
	Local/pain	Burning at the site of injection	11	30	*Dhanani 2012*
			0	65	*Nanthini 2017*
		Local pain	30	75	*Kumar 2005*
			6	50	*Singh 2012*
			23	65	*Nanthini 2017*
	Muscular	Arthralgia	2	75	*Kumar 2005*
	Nervous system	Headache	6	65	*Nanthini 2017*
		Immediate headache and giddiness	2	75	*Kumar 2005*
		Giddiness	4	30	*Dhanani 2012*
		Shivering and weakness	0	50	*Singh 2012*
	Other	Regional lymphadenopathy	5	65	*Nanthini 2017*
		Side effects	40	75	*Kumar 2005*
	Systemic	Systemic ache	6	75	*Kumar 2005*
	Vascular	Local phlebitis	0	50	*Singh 2012*
IPMCX	**General**	Bronchospasm	0	41	*Ortiz 2011*
		Pruritus	0	41	*Ortiz 2011*
	GI	Abdominal pain	0	41	*Ortiz 2011*
		Constipation	1	41	*Ortiz 2011*
		Diarrhoea	4	41	*Ortiz 2011*
		GI upset*	13	45	*Al 2005*
		Epigastric pain	1	41	*Ortiz 2011*
		Nausea	7	41	*Ortiz 2011*
		Vomiting	2	41	*Ortiz 2011*
	Nervous System	Headache	4	41	*Ortiz 2011*
	Pain	Back pain	0	41	*Ortiz 2011*
IVIDX	**Cardiac**	Low blood pressure	1	105	*Tariq 2015*
		Palpitation	1	105	*Tariq 2015*
	General	Heat intolerance	1	105	*Tariq 2015*
	GI	Abdominal cramps	0	27	Symonds 1969
		Constipation	0	33	Darwish 2017
			1	27	Symonds 1969
		Epigastric discomfort	0	33	Darwish 2017
		Nausea	0	33	Darwish 2017
		Nausea and vomiting	0	27	Symonds 1969
		Vomiting	0	33	Darwish 2017
	Local	Local injection site inflammation	1	33	Darwish 2017
	Muscular	Small joint stiffness	1	105	Tariq 2015
	Nervous system	Shivering	2	105	Tariq 2015
	Other	Other symptoms	2	27	Symonds 1969
	Systemic	Allergic reaction	1	33	Darwish 2017
IVIFCM	**Biomarkers**	High level of serum transaminases at 3wks	1	50	*Jose 2019*
		Hypophosphatemia (early treatment)	2	50	*Jose 2019*
	General	Dysgeusia	2	123	*Breymann 2016*

		Rash	0	123	*Breymann 2016*
		Bronchospasm	1	123	*Breymann 2016*
	GI	Abdominal pain	0	123	Breymann 2016
		Epigastric pain	NR	50	Jose 2019
		Constipation	0	123	*Breymann 2016*
		Diarrhoea	0	123	*Breymann 2016*
		Dyspepsia	0	123	*Breymann 2016*
		GI upset	3	123	*Breymann 2016*
		Nausea	2	123	*Breymann 2016*
		Vomiting	0	123	*Breymann 2016*
	Local/reaction	Injection site reaction/inflammation/swelling	1	50	*Jose 2019*
	Nervous System	Dizziness	3	123	*Breymann 2016*
		Headache	4	123	*Breymann 2016*
		Nervous system disorders	7	123	*Breymann 2016*
		Syncope	0	123	*Breymann 2016*
	Other	General disorders & administration-site conditions	4	123	*Breymann 2016*
		Anaphylactic reaction	0	80	*Rajwani 2020*
		Refused treatment	2	80	*Rajwani 2020*
	Vascular	Vascular disorders	2	123	*Breymann 2016*
		Venous thrombosis	0	80	*Rajwani 2020*
IVISU	**Biomarkers**	Hypophosphatemia (early treatment)	3	50	*Jose 2019*
	Cardiac	Bradycardia	1	970	*Neogi 2019*
		Hypotension	3	970	*Neogi 2019*
		Hypertension	1	970	*Neogi 2019*
		Syncope	1	970	*Neogi 2019*
		Tachycardia	0	62	*Nanthini 2017*
			1	75	*Arzoo 2020*
		Venous Thrombosis	0	80	*Rajwani 2020*
	General	Chest compression	3	970	*Neogi 2019*
		Fever	1	52	*AlMomen 1996*
			1	25	*Aggarwal 2012*
			0	50	*Gupta 2014*
			5	75	*Mehta 2014*
			2	62	*Nanthini 2017*
		Immediate AE	21	970	*Neogi 2019*
		Late AE	79	970	*Neogi 2019*
			2	100	*Rudra 2016*
			1	75	*Dalal 2018*
		Heat intolerance	1	93	*Tariq 2015*
		Hot flush	2	100	*Deeba 2012*
		Hypotensive or hypertensive response	0	25	*Aggarwal 2012*
		Itching all over body (pruritus)	1	50	*Abhilashini 2014*
			0	50	*Gupta 2014*
			1	100	*Rudra 2016*
			5	75	*Dalal 2018*
			2	970	*Neogi 2019*
		Low blood pressure	1	93	*Tariq 2015*
		Metallic taste	0	50	*Abhilashini 2014*
			5	100	*Deeba 2012*
			2	50	*Gupta 2014*
	General		0	75	*Mehta 2014*
		Immediate AE	6	970	*Neogi 2019*
		Late AE	0	970	*Neogi 2019*
			NR	100	*Rudra 2016*
		Altered Taste	4	25	*Aggarwal 2012*

	Palpitation	2	93	*Tariq 2015*
	Regional lymphadenopathy	0	62	*Nanthini 2017*
	Tightness and discomfort in the skin	1	52	*AlMomen 1996*
GI	Abdominal pain	2	50	*Jose 2019*
		1	50	*Singh 2012*
		1	75	*Arzoo 2020*
	Epigastric discomfort /Nausea/ Vomiting	0	75	*Mehta 201*
	Epigastric discomfort and bloating	NR	100	*Rudra 2016*
	Abdominal discomfort	10	50	*Gupta 2014*
	Constipation	0	50	*Abhilashini 2014*
		0	25	*Aggarwal 2012*
		9	50	*Gupta 2014*
		2	50	*Kochhar 2013*
		4	970	*Neogi 2019*
	Constipation/ Diarrhoea	0	75	*Mehta 2014*
	Diarrhoea	0	50	*Abhilashini 2014*
		0	25	*Aggarwal 2012*
		0	24	*AlMomen 1996*
		1	24	*Bayoumeu 2002*
		0	56	*Bhavi 2017*
		0	100	*Deeba 2012*
		1	50	*Gupta 2014*
		0	50	*Kochhar 2013*
		10	970	*Neogi 2019*
		NR	100	*Rudra 2016*
	Dyspepsia	0	50	*Abhilashini 2014*
	Gastritis	0	25	*Aggarwal 2012*
		0	56	*Bhavi 2017*
		0	30	*Dhanani 2012*
		4	970	*Neogi 2019*
	Heartburn	1	50	*Kochhar 2013*
	Hiccup	0	50	*Kochhar 2013*
	Nausea and/or vomiting	0	50	*Abhilashini 2014*
		0	25	*Aggarwal 2012*
		4	100	*Deeba 2012*
		0	50	*Kochhar 2013*
		0	56	*Bhavi 2017*
		0	30	*Dhanani 2012*
		1	50	*Gupta 2014*
		2	62	*Nanthini 2017*
	Nausea	4	100	*Rudra 2016*
	Vomiting	NR	100	
	Nausea (immediate AE	20	970	*Neogi 2019*
	Vomiting (immediate AE)	14	970	*Neogi 2019*
	Nausea (late AE	14	970	*Neogi 2019*
	Vomiting (late AE)	46	970	*Neogi 2019*
	GI upset	6	45	*Al 2005*
		0	52	*AlMomen 1996*
		0	100	*Deeba 2012*
Local/discoloration	Skin staining at injection site	0	30	*Dhanani 2012*
		0	62	*Nanthini 2017*
	Skin staining at injection site	0	50	*Singh 2012*
Local/pain	Burning/pain at the site of injection	6	56	*Bhavi 2017*
		1	30	*Dhanani 2012*
		0	50	*Gupta 2014*
		15	75	*Mehta 2014*
		11	62	*Nanthini 2017*

			0	50	*Singh 2012*
	Local/reaction	Injection site reaction/inflammation/swelling	1	30	*Dhanani_2012*
			2	50	*Jose 2019*
			3	62	*Nanthini 2017*
			4	100	*Rudra 2016*
	Local/vascular	Local phlebitis	2	50	*Singh 2012*
	Muscular	Arthralgia	1	100	*Deeba 2012*
			20	970	*Neogi 2019*
			1	100	*Rudra 2016*
		Small joint stiffness	5	93	*Tariq 2015*
	Nervous System	Dizziness	1	100	*Deeba_2012*
		Giddiness	0	30	*Dhanani 2012*
		Headache	0	25	*Aggarwal 2012*
			0	50	*Kochhar 2013*
			3	62	*Nanthini 2017*
			52	970	*Neogi 2019*
			3	75	*Dalal 2018*
		Shivering	1	93	*Tariq 2015*
		Shivering and weakness	1	50	*Singh 2012*
	Other	Could not tolerate drug	0	52	*AlMomen 1996*
		Not-unpleasant taste during injection	1	24	*Bayoumeu 2002*
		Serious Adverse Events	0	40	*NCT00746551*
			0	100	*Rudra 2016*
		Side effects	6	45	*Neeru 2012*
	Pain	Myalgia	1	50	*Abhilashini 2014*
			49	970	*Neogi 2019*
		Arthritis	1	25	*Aggarwal 2012*
	Systemic	Anaphylaxis Grade 1	2	25	*Aggarwal 2012*
		Anaphylaxis Grade 2	0	25	*Aggarwal 2012*
		Anaphylactic reaction	0	970	*Neogi 2019*
	Vascular	Phlebitis	6	75	*Mehta 2014*
		Thrombophlebitis	1	25	*Aggarwal 2012*
			0	50	*Gupta 2014*
			43	970	*Neogi 2019*
LAC	**GI**	Abdominal pain	1	49	*Nappi 2009*
			20	100	*Rezk 2016*
			5	50	*Gawai 2020*
		Constipation	1	49	*Nappi 2009*
			20	100	*Rezk 2016*
			7	50	*Gawai 2020*
		Dark stools	0	100	*Rezk 2016*
			0	50	*Gawai 2020*
		Diarrhoea	0	49	*Nappi 2009*
		GI upset	10	100	*Rezk 2016*
			15	50	*Gawai 2020*
		Nausea and/or vomiting	1	49	*Nappi 2009*
			10	100	*Rezk 2016*
			9	50	*Gawai 2020*
LAC	**Other**	Want to stop intake	0	100	*Rezk 2016*
		Acceptability	48	50	*Gawai 2020*
NOFE	**GI**	Abdominal cramps	0	27	*Symonds 1969*
		Constipation	4	27	*Symonds 1969*
		Nausea and/or vomiting	1	27	*Symonds 1969*
	Other	Other symptoms	1	27	*Symonds 1969*

***IAAC**, iron amino acid chelate; **IFS**, ferrous sulphate; **FASG**, ferrous asparto glycinate; **ICARB**, carbonyl iron; **ICSAC**, iron chondroitinsulfuric acid complex; **IFA**, ferrous ascorbate; **IFF**, ferrous fumarate; **IFG**, ferrous gluconate;*

***IMISCA**, intramuscular iron sorbitol citric acid; **IPMCX**, Iron polymaltose complex; **IVIDX**, intravenous iron dextran; **IVIFCM**, intravenous ferric carboxymaltose; **IVISU**, intravenous iron sucrose; **LAC**, Lactoferrin; **NOFE**, "no-iron intervention" (placebo/vitamin/no intervention); **NR,** non reported.*

Appendix 10 Upcoming trials evaluating effect of iron preparation in iron deficient anaemia in pregnancy

Clinical trial CT registration ID	Country	Comparison	Sample size	Outcomes
NCT00802139	South Korea	Iron acetyl-transferase vs Iron sucrose	58	Change in Hb level a achievement rate (11g saturation, Sf, TIBC, change in reticulocyte
NCT03481790	Egypt	Lactoferrin vs Ferrous sulphate + Folic Acid	200	Hb at 4 wks, Sf at 4 v
NCT02086838	Egypt	Theragran Hematinic vs iron dextran (IV)	212	The proportion of pat successfully treated a participants with adve
NCT03484845	Egypt	Lactoferrin vs Ferrous fumarate	150	Increase in blood Hb
NCT03657433	US	Ferumoxytol (IV) vs Ferrous sulphate	140	Change in Hb, Chang laboratory values, ma outcomes
NCT04278651	US	Ferumoxytol (IV) vs Ferrous sulphate	80	Change in Hb level a resolution, Anemia at Adherence, Need for transfusion, neonatal
NCT04253626	US	Ferumoxytol (IV) vs Ferrous sulphate	80	Change in Hb level a
NCT03202615	Egypt	Lactoferrin vs Ferrous sulphate	130	Change in Hb (1, 2 m (1, 2 mths), change in parameters, cost, safe
NCT03188445	Denmark	Iron Isomaltoside (IV) vs Ferrous fumarate with vitamin C	201	Achievement of Hb ≥ Achievement of Hb ≥ time points, change in
NCT03438227	US	Ferrous sulphate vs iron dextran (IV)	120	Hb at delivery, mater outcomes, safety, blo
NCT03456258	Egypt	Lactoferrin vs Ferrous fumarate	100	Hb at 8 wks, Sf at 8 v
ACTRN12617001634369	Bangladesh	Lactoferrin vs Ferrous sulphate	608	Hb at 24 & 34 wks of & 34 wks of gestation values, maternal and adherence, safety
Clinical trial CT registration ID	**Country**	**Comparison**	**Sample size**	**Outcomes**
ACTRN12614000988651	Australia	Lactoferrin vs Ferrous sulphate	800	Change in Hb, Chang laboratory values, ma outcomes, quality of
EudraCT 2017-000994-35	Spain	Ferric pyrophosphate vs Ferrous sulphate	130	Efficacy, Quality of l perinatal outcomes
EudraCT 2010-018940-15	Germany	Ferrous (II) glycine sulphate complex vs IFG	40	Change in Hb
CTRI/2019/02/017553	India	Ferric carboxymaltose (IV) vs Iron sucrose (IV)	100	Improvement in anae haematological assess safety, maternal and i
CTRI/2018/12/016771	India	Ferric carboxymaltose (IV) vs Iron sucrose (IV)	200	Hb and Sf at 4 & 8 w iron, RBC indices, ne transfusion, perinatal postpartum haemorrh transfusion
CTRI/2018/12/016537	India	Tab-Dhatrilauha vs cap-Autrin	100	Sf, Serum total iron b

CTRI/2017/06/008884	India	Ferric carboxymaltose (IV) vs Ferrous sulphate	173	No details available
CTRI/2015/07/006049	India	Dhatri Lauha vs Punarnava Mandura vs Ferrous sulphate	35	Improvement in signs Garbhini Pandu, Incr
CTRI/2014/01/004369	India	Ferric carboxymaltose (IV) vs Iron sucrose (IV)	230	Hb (mean change) at
CTRI/2013/11/004142	India	Iron sucrose (IV) vs Ferrous sulphate	100	No details available
CTRI/2009/091/001077	India	Iron sucrose (IV) vs Ferrous fumarate	100	Improvement in bloo reticlocyte response, Clinical improvemen

Hb, haemoglobin; Sf, serum ferritin; wks, weeks; IV, intravenous; RBC, red blood cell