Iron preparations for women of reproductive age with iron deficiency anaemia in pregnancy (FRIDA)

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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 (IDA) in pregnancy. Our aim was to determine the relative effect of iron preparations used to treat IDA in pregnancy.

Methods

We conducted a systematic review with network meta-analysis (NMA) of randomised trials. We searched Medline, Embase, Cochrane Central Register of Controlled Trials, trial registers and grey literature up to 28th February 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. Two independent reviewers selected studies, extracted data, and carried out a risk of bias assessment using 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. We performed random-effects pairwise and network meta-analyses. The effect measure is reported as mean difference (MD) with 95% confidence intervals (CI). This study is registered with PROSPERO, number CRD42018100822.

Findings

Of the 53 eligible trials, 30 (15 interventions; 3,243 women) and 15 (nine; 1,396) contributed data to comparisons on haemoglobin and serum ferritin respectively. The risk of bias varied across the trials contributing to NMA. Compared with ferrous sulphate, 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 ferric carboxymaltose (8·52 g/L, 0·51-16·53) improved haemoglobin levels. The evidence for other interventions was insufficient. There were no appreciable differences in rates of side effects between individual iron preparations.

Interpretation

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

Funding

This work did not receive any funding.

Word count: 299/300 words

Research in context

Evidence before this study

Iron deficiency anaemia is common in pregnancy due to increasing iron demands and is associated with adverse maternal and perinatal outcomes. There are numerous iron preparations are available for the treatment, however these have only been compared in traditional pairwise meta-analyses, the most comprehensive being two published Cochrane reviews, one in 2011 and another in 2015. Prior to undertaking this work, we carried out searches in Pubmed, Embase, The Cochrane Library and the PROSPERO database of registered systematic reviews to look for completed or ongoing systematic reviews and network meta-analyses of iron treatments for anaemia in pregnancy (search carried out in February 2018). Our inclusion criteria were systematic reviews with a network meta-analysis of iron interventions for the treatment of anaemia in pregnancy. As we found no published network meta-analyses or available protocols no quality assessment was undertaken.

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. Secondly, this work updates existing meta-analyses assessing the effectiveness of iron interventions in pregnant women.

Implications of all the available evidence

Treating 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 existing policy on treatment of anaemia in pregnancy should be updated to demonstrate the effectiveness of the available preparations against each other, so women and clinicians can make informed choices.

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 1, pages 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] Exclusion criteria are available in Appendix 2 (page 12). We had originally planned to evaluate the effect of iron preparations in three separate populations: menstruating women, pregnant women and postpartum. In this paper we present the findings for the pregnant population only. 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] Thus the literature search was run from 1st January 2011 to 19th July 2018 using a modified search strategy (Appendix 3, page 15); updated to 28th February 2021. A search, without any language limits, was performed in the major medical literature databases (Appendix 2, page 12). Additionally, we checked the Inside Conferences, Systems for Information in Grey Literature database for grey literature, clinical trial registers for ongoing trials (Appendix 2, page 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 2, page 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 sulphate, 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 1, page 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 9,145 women were included (Figure 1). The main reasons for exclusion were non-RCT design (n=25), 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 the majority of women having moderate anaemia (67/109 trial arms with haemoglobin ranging from 99 to 70 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 4 (pages 16-22). Overall, we included trials evaluated 19 different 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 4, pages 23-29).

Of all included trials, 30 (62 arms; 3,243 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 2). Five comparisons were evaluated in more than one study and the other comparisons were evaluated in a single trial (Figure 2). IV iron sucrose vs ferrous sulphate were the most frequently compared pair of interventions (seven trials, 695 women), followed by lactoferrin vs ferrous sulphate (four trials, 457 women), and ferrous fumarate vs IV iron sucrose (four trials, 305 women) (Figure 2a; Appendix 5, page 30).

The risk of bias varied across the trials contributing to the network meta-analysis. Random sequence generation was correctly implemented in half of the trials (12/25, 48%). Allocation concealment frequently could not be assessed due to insufficient information (19/25, 76%), blinding of staff and participants was assessed as low risk of bias in 60% of the included trials (15/25). Incomplete outcome data was deemed at low risk in 68% (17/25) and selective reporting of outcomes 72% (18/25) of the trials. The indirectness of the study population included in the included trials was assessed as medium in three trials (3/25, 12%). An overview of the network for haemoglobin by the global risk of bias of the trials informing the results can be found in Appendix 6a (page 32). Trials not included in the network meta-analysis were more often assessed as at high risk of bias (Appendix 6b, pages 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). There was insufficient evidence of improvement of haemoglobin levels between the other interventions and

iron ferrous sulphate (Figure 3a). There was no evidence to suggest global (chi-squared = 1·67, p-value = 0·43) or local inconsistencies (Appendix 7, page 35). The direct and network effects (indirect and direct evidence) were consistent for the majority of comparisons. Interventions with the highest SUCRA were iron ferrous asparto glycinate (84·9%), IV ferric carboxymaltose (80·6%) and IV iron sucrose (77·7%), while non-iron preparation had the lowest SUCRA (21·6%) (Appendix 7, page 37). The detailed ranking measures, including SUCRA and mean rank, are presented in Appendix 7 (pages 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 8, pages 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 8, pages 50-52). Network meta-analysis based on trials from high income countries was not performed due to the small number of studies in this subgroup. 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 8, pages 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.

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 7, page 36). Interventions with the highest SUCRA were IV iron sucrose (81·9%) and IV ferric carboxymaltose (74·4%) (Appendix 7, page 38). The detailed ranking measures, including SUCRA and mean rank, are presented in Appendix 7 (pages 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 Appendix 9 (pages 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 10, pages 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 individual 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 10, pages 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.

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.

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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Tables

Figures

Appendices