

Testing equivalence of two doses of intravenous iron to treat iron deficiency in pregnancy: A randomised controlled trial

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Abstract

Objective To test equivalence of two doses of intravenous iron (ferric carboxymaltose) in pregnancy. **Design** Parallel, two-arm equivalence randomised controlled trial with an equivalence margin of 5%. **Setting** Single centre in Australia. **Population** 278 pregnant women with iron deficiency. **Methods** Participants received either 500 mg (n=152) or 1000mg (n=126) of intravenous ferric carboxymaltose in the second or third trimester. **Main outcome measures** The proportion of participants requiring additional intravenous iron (500mg) to achieve and maintain ferritin >30ug/L (diagnostic threshold for iron deficiency) at 4 weeks post-infusion, and at 6 weeks, and 3-, 6- and 12-months postpartum. **Secondary endpoints** included repeat infusion rate, iron status, birth, and safety outcomes. **Results** The two doses were not equivalent within a 5% margin at any timepoint. At 4 weeks post infusion, 26/73 (36%) participants required a repeat infusion in the 500 mg group compared with 5/67 (8%) in the 1000 mg group (difference in proportions, 0.283 95% confidence interval (0.177, 0.389)). Overall, participants in the 500 mg arm received twice the repeat infusion rate (0.81 (SD= 0.824 vs 0.40 (SD= 0.69), rate ratio 2.05, 95% CI (1.45, 2.91)). **Conclusions** Administration of 1000mg ferric carboxymaltose in pregnancy maintains iron stores and reduces the need for repeat infusions. A 500 mg dose requires ongoing monitoring to ensure adequate iron stores are reached and sustained.

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Running title: Dose finding study to establish optimal iv iron dose in pregnancy

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Results

The two doses were not equivalent within a 5% margin at any timepoint. At 4 weeks post infusion, 26/73 (36%) participants required a repeat infusion in the 500 mg group compared with 5/67 (8%) in the 1000 mg group (difference in proportions, 0.283 95% confidence interval (0.177, 0.389)). Overall, participants in the 500 mg arm received twice the repeat infusion rate (0.81 (SD= 0.824 vs 0.40 (SD= 0.69), rate ratio 2.05, 95% CI (1.45, 2.91)).

Conclusions

Administration of 1000mg ferric carboxymaltose in pregnancy maintains iron stores and reduces the need for repeat infusions. A 500 mg dose requires ongoing monitoring to ensure adequate iron stores are reached and sustained.

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Keywords

Randomised controlled trials, Antenatal care, Medical disorders in pregnancy, Haematology: Anaemia, Obstetric haemorrhage, Risk management

Tweetable abstract

Australian trial finds optimal dose of intravenous iron in pregnancy to reduce risk of recurrent deficiency

Trials Registry, ACTRN12615000950561 <https://www.anzctr.org.au>

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Introduction

Iron deficiency (ID) is the most common nutritional disorder worldwide, listed on the World Health Organisation's (WHO) top 5 mental and physical disabilities.(1) ID is the leading underlying cause of anaemia, affecting approximately 45% of women of childbearing age in developed countries and up to 80% in lower resource settings.(2) As iron is necessary for many biological functions (3, 4) pregnant women with ID or iron deficiency anaemia (IDA) frequently suffer from cardiovascular problems, reduced physical activity, impaired cognitive performance, reduced immune function, fatigue and depressive episodes.(3, 5, 6) These women are at a higher risk of pregnancy complications, stillbirth, postpartum haemorrhage (PPH), peri-partum allogeneic red blood cell transfusion and death.(7-11) Infants of mothers with ID are at increased risk of preterm birth, growth restriction, low birth weight, perinatal death, low Apgar scores, neonatal infection, postnatal ID and impaired cognitive development.(4, 7, 9, 12) In recognition of these adverse outcomes, WHO targets 50% reduction of IDA in women of reproductive age by 2025.(13)

Women with inadequate iron stores are ill-prepared for the increased iron demand of pregnancy,(14) rendering up to 47% of pregnant women iron deficient.(15) ID is detectable, preventable and treatable,(3) with oral iron considered first-line treatment. Intravenous iron (IVI) is recommended when women are non-responsive, non-tolerant or non-compliant to oral iron, when ID/IDA is diagnosed late in pregnancy, or in women with severe anaemia or at risk of haemorrhage.(16-20)

Randomised controlled trials (RCTs) in pregnant women with IDA have demonstrated superior haematological outcomes after IVI compared with oral iron.(16, 21-23) Doses of IVI in RCTs and observational studies have ranged from 400mg to 1000mg, with all showing improvements in iron status without serious safety concerns.(16, 21-23) Higher doses come at a larger cost, and no data exist comparing adverse effects or the potential for iron excess with different doses.(24) In addition, accessibility to IVI and approved dosing schemes differ between countries, creating geographic, cultural and social barriers.(4, 25) Clinicians lack high quality data on the optimal dose to adequately improve and sustain iron status, and sufficiently protect against adverse obstetric, neonatal or mental health sequelae. We therefore conducted a RCT comparing two doses of IVI (500mg and 1000mg) using an equivalence design.

Methods

This was a single centre, randomised, parallel, two-arm equivalence study with an equivalence margin of 5%. The equivalence design was chosen due to uncertainty about optimal dosing strategies in clinical management of anaemia in pregnancy. The margin was determined via clinical consensus of the organisation's anaesthetic team. The trial was approved by the Northern Adelaide Local Health Network ethics committee (HREC/14/TQEH/LMH/122). All patients provided written informed consent.

Patients

Pregnant women aged over 18 years in the second or third trimester with ID, defined as ferritin [?] 15 µg/l and a transferrin saturation < 25% were eligible. Participants were excluded if they had untreated B12 or folate deficiencies, known hypersensitivity to FCM, haemoglobin >130 g.l⁻¹; serious medical condition, uncontrolled systemic disease, or inability to fully comprehend or perform study procedures. Women were screened for ID during routine antenatal assessment at the Women's Assessment Unit at the Lyell McEwin Hospital, Elisabeth Vale, South Australia.

Randomisation

Randomisation was performed by a trial pharmacist using an online randomisation sequence generator and opaque envelopes. Participants were stratified into two arms based on their haemoglobin at time of screening, $< 105 \text{ g.l}^{-1}$ or $[?] 105 \text{ g.l}^{-1}$. Study participants, clinicians, researchers, and statistician were masked to treatment allocation until after all analyses were complete.

After data review at trial completion, 14 ineligible participants were discovered to have been mistakenly enrolled and randomised. These participants were excluded from the analysis (Figure 1); this is not expected to cause bias. (26)

Interventions

The intervention was intravenous ferric carboxymaltose (FCM), 500 mg or 1000mg, in 250ml of normal saline, infused over 30 minutes. At the first appointment after screening, FCM at the randomised dose was administered.

Iron status was monitored at five study timepoints: 4 weeks after the initial infusion, then at 6 weeks-, 3-, 6- and 12- months postpartum, or at the time of next pregnancy, whichever came first. The diagnostic criteria indicating persistent ID and requiring additional IVI were ferritin $< 30 \mu\text{g/l}$ plus transferrin saturation $< 25\%$, or, if inflammation were present (CRP $> 7.9 \text{ ng/l}$), ferritin between 30 and $50 \mu\text{g/l}$ plus a transferrin saturation $< 20\%$. If confirmed, ID was treated with a single 500mg FCM infusion in both groups.

Endpoints

The primary endpoint was the proportion of participants requiring additional intravenous FCM to maintain successful correction of ID, based on the diagnostic criteria. Patients were assessed at the five timepoints. Where participants conceived at any time during their follow-up, they were assessed for their final follow up appointment and exited the study.

Secondary endpoints were repeat infusion rate prior to delivery, after delivery and overall during the study period, iron and haematological outcomes (serum iron, ferritin, transferrin and transferrin saturation), maternal pregnancy outcomes and complications (including gestational diabetes), pre-eclampsia, gestational hypertension, preterm labour, pre-labour rupture of membranes, preterm pre-labour rupture of membranes (PPROM), preterm birth, gestational age at birth, antenatal haemorrhage, postpartum haemorrhage, mode of delivery), neonatal outcomes (birth weight, customized birth weight centile, birth length and head circumference) and child neurodevelopment at 12 months of age (Ages and Stages Questionnaire- Third Edition; ASQ).(27) Additional infusions, iron and haematological outcomes were evaluated at the five timepoints.

Sample Size

The study was designed assuming 12% of participants in each treatment arm would require a repeat iron infusion.(28) Using an equivalence margin of 5% and a power of 80%, 131 participants were required in each arm at baseline. After accounting for an expected 15% drop out, the required sample size was 151 in each arm of the study.

Statistical analysis

Patient characteristics were described using means (standard deviation), medians (interquartile range), or counts and frequencies, as appropriate. Primary and secondary endpoints were analysed using regression models with treatment group and haemoglobin at baseline ($\text{Hb} < 105$ or $\text{Hb} [?] 105$) as covariates. Endpoints measured at multiple timepoints were analysed using repeated measures models with a timepoint by treatment group interaction. All analyses were performed in SAS v 9.4 (SAS Institute, Cary NC USA) or R v4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Primary endpoint: The difference in proportions of participants who required a repeat iron infusion at each timepoint was analysed using a repeated measures model with generalized estimating equations (GEEs) and an independence working correlation.

Two one-sided tests at the 0.05 level were used to assess equivalence at each time point. Since the equivalence margin was 5%, 90% confidence intervals for absolute differences in proportions between groups at each time point were examined as to whether they lay within the interval (-0.05, 0.05). To establish equivalence, the proportion of participants in both groups must lie completely within this interval.

Secondary endpoints: Repeat infusion rates were analysed using Poisson regression models. Serum iron, transferrin, and transferrin saturation were analysed using mixed effects linear regression models adjusted for baseline. The measurement of ferritin at baseline was subject to threshold effects from limits to detection ($<4 \mu\text{g/l}$) and was singly imputed half the limit of detection ($2 \mu\text{g/l}$).

Maternal pregnancy and birth complications, mode of delivery and neonatal outcomes were analysed using linear or logistic regression models, as appropriate. GEEs with an independence working correlation structure were used, where relevant, to account for multiple births.

For secondary clinical outcomes, we report mean differences (MDs) in the change from baseline between treatment groups, rate ratios (RRs) or odds ratios (ORs), as appropriate, with 95% confidence intervals (CI).

Sensitivity analyses

A number of sensitivity analyses were conducted on the primary outcome. Treatment effects were also estimated using a linear mixed model with autoregressive correlation. Post-hoc sensitivity analyses used an autoregressive or exchangeable correlation structure with GEEs.

A further post-hoc sensitivity analysis was performed at all timepoints using the same analysis as the primary outcome. Since the intervention was only administered in a clinical setting, the outcome was whether a repeat infusion was administered or not; any participants who did not present for a follow-up appointment were coded as not having received a repeat infusion. Finally, the difference in proportions of participants who (1) received an infusion whether it was required or not and (2) received an infusion per protocol was analysed.

As a secondary post-hoc analysis, the primary outcome was estimated using all randomised participants to assess the possibility of bias and the effect of reduced power after ineligible participants were excluded.

Results

Between 26/05/2015 and 14/08/2017, 1,182 women were screened for trial eligibility at our antenatal assessment unit. A total of 304 women were randomised, nine participants withdrew prior to the infusion, two did not receive the infusion and one entered labour before the infusion. 292 participants received an infusion and 278 were included in the analysis. The trial flow is shown in Figure 1.

The demographic and clinical characteristics of study participants at baseline are presented in Table 1. Participants were enrolled into the trial on average at 32 weeks gestational age. Approximately half of all participants were anaemic at study entry. The first infusion was received on average 11-12 days after screening.

The proportion of participants assigned to the two different trial doses of IVI were not equivalent within a 5% margin at any time point (Table 2). More participants assigned to 500mg IVI required repeat infusions at 4 weeks post infusion compared to those assigned to 1000mg IVI (26/73 (36%) vs 5/67 (8%); estimated difference in proportions, 0.28, 90% CI (0.18, 0.39)). Between 4 weeks post infusion and 6 months postpartum, the difference between the groups reduced but the 90% confidence interval did not lie within (-0.05, 0.05), therefore equivalence was not achieved within a 5% margin (15/88 (17%) vs 9/67 (13%) at 6 months postpartum; estimated difference in proportions 0.037, 90% CI (-0.059, 0.133)) (Figure 2). The proportion of participants requiring a repeat infusion increased over time in the 1000mg IVI group from 5/67 (8%) at 4 weeks post infusion to 14/70 (20%) at 12 months postpartum. Equivalence was not achieved in the sensitivity analyses using linear mixed models, GEEs with different correlation structures, participants who received repeat infusions or were treated per protocol (Table S1) and the secondary analysis of all randomised participants (Table S2). The proportion of participants who required a repeat infusion at any time during

follow-up was also not equivalent (83/152 (55%) vs 34/126 (27%), estimated difference in proportions 0.288, 90% CI (0.191, 0.384)) (Table S1).

Compared to participants assigned to 1000mg IVI, participants in the 500mg IVI received more than twice the repeat infusion rate prior to delivery, after delivery and overall (0.81 (0.84) vs 0.40 (SD= 0.69), Rate Ratio 2.05, 95% CI (1.45, 2.91), $p < 0.001$) (Table 3).

Participants who received 1000mg IVI had significantly higher ferritin levels up to 6- months postpartum, compared to those receiving 500mg IVI (Table 3). Similarly, serum iron and transferrin saturation were higher in participants who received 1000mg IVI than participants who received 500mg IVI at 4 weeks post infusion, while transferrin was lower (Table 3). Between group differences had disappeared for all markers of iron status by 12 months postpartum.

No serious adverse events were observed. Minor adverse events were observed in 3% (n=8/276, 2 with missing data) of all participants during the first infusion, including 5/126 participants (4%) who received 1000mg iron (dizziness n=2, hypotension n=1, nausea n=1, chest tightness n=1) and 3/150 participants (2%) who received 500mg iron (nausea n=2, hypotension n=1). There was no difference between the groups (Fisher's exact test, $p=0.48$). No adverse events were observed on subsequent infusions.

PPROM occurred in 6/121 participants in the 1000mg arm only. The likelihood of other maternal complications did not differ between participants who received 500mg and 1000mg IVI (Table 3). Similarly, no difference was found between the length of gestation, neonatal outcomes, or child neurodevelopment between the two doses (Table 3).

A post-hoc analysis of haemoglobin levels indicated these were significantly higher in participants in the 1000mg IVI group compared to the 500mg IVI at 4 weeks post infusion (Table S3). At each time point, the mean Hb level was in a range indicating sufficiency (>115) in both the 500mg and 1000mg IVI iron groups.

Main Findings

This randomised controlled trial, comparing two pragmatic doses of intravenous iron for treating ID in pregnancy, demonstrated 500 mg of intravenous FCM was not equivalent to the 1000 mg dose. To achieve initial and sustained correction of ID, participants in the lower dose arm received more than twice the rate of repeat infusions compared to the higher dose arm. Participants in the higher dose arm had significantly higher ferritin levels up to 6 months postpartum, coupled with a significantly greater increase in haemoglobin, reflecting favourable iron availability and utilisation. While participants in the lower arm also remained iron replete for the duration of the study, this occurred under close monitoring with appropriate treatment administered where declining iron stores were observed, as per our study protocol. Given the rate of persistent ID observed in this group, we would suggest that continued monitoring after infusion of 500g IVI is essential to ensure adequate iron stores are accomplished in pregnancy.

The ability of IVI to improve antenatal and postpartum haematological outcomes in pregnant women has been demonstrated in several previous randomised controlled trials.(16, 21-23) These studies have used a range of IVI dosing strategies to achieve vital short-term iron repletion and haemoglobin restoration in anaemic women, using doses ranging from 400mg to 1000mg.(16) The current study, is to our knowledge, the first prospective RCT to compare intravenous iron doses for successful and persistent correction of ID in pregnancy and over the first postpartum year. Recent concerns have been raised whether IVI prescribing practice for women of reproductive age is appropriate and cost effective.(24) Our data suggest administration of 1000mg can significantly reduce the need for repeat IVI, thereby improving patient health while reducing clinical load and cost. The importance has become even more apparent during the COVID-19 pandemic. Globally, antenatal services were disrupted and fear of contracting the virus led to a decrease of antenatal visits.(29) Australia saw a 8.3% reduction in face-to-face antenatal care services for 2020 compared with 2019.(30) However, it is imperative that clinicians and patient do not become complacent after IVI administration, given over 20% of participants in both arms required additional infusions at 12 months postpartum to sustain satisfactory iron stores.

ID and IDA are significant medical conditions with serious consequences for maternal and fetal outcomes.(3, 7, 8, 13) Our study found no differences in pregnancy, birth- or infant related outcomes between the 500mg and 1000mg IVI arms, with the exception of PPRM, which occurred only in participants receiving 1000mg. Although the pathways leading to PPRM are complex and multifaceted, increased oxidative stress appears to play a role. It is possible that first or second trimester IDA itself, or exposure to increased iron, or differences in ferritin levels after IVI, may have contributed to oxidative stress leading to PPRM in the current study.(31) However, this must be interpreted with caution given the present study was not powered to examine this outcome.

Pregnancy represents a time of increased iron demand.(4) The prevalence of ID is high, and progression from ID to IDA common.(20) Ensuring iron stores are optimal throughout pregnancy can avoid any adverse physiological and psychological outcomes associated with ID and IDA .(20, 32) Further, should women experience a PPH, which remains the leading cause of maternal morbidity and mortality, optimal iron stores will boost Hb, which can provide a buffer to help protect against serious anaemia.(33) Although routine in our obstetrics unit, screening for ID is rarely incorporated into routine antenatal care.(34) Recent obstetrics guidelines on the management of ID and obstetric patient blood management guidelines have emphasised the need for more attentiveness and potential actions to detect and treat ID in pregnancy.(19, 20) Despite this, IVI therapy has continued to be met with fear, scepticism, and criticism, resulting in large uptake variations.(16, 22, 23, 35-38)

Strengths and Limitations

The strengths of this study include the blinding of clinician, health care team, patient, and statistician, the long follow-up period, including longer-term assessment of child health. The findings can reassure obstetric teams of the safety, efficacy, and comprehensive benefits of IVI iron to treat ID and IDA in pregnancy.

The limitations include the variable number of participants who returned for each post infusion appointment. This is particularly relevant for the 4 weeks post infusion time point, where only around 50% of participants in each arm attended. To address this, we conducted a post-hoc sensitivity analysis assessing the number of participants receiving an infusion as a function of the total number of participants in each arm, assuming that patients who did not attend an appointment did not require an infusion. The results supported our non-equivalence findings. Although our trial was conducted at a single site, we observed changes in all blood markers of iron status over the study period biologically consistent with a difference in the ability of both doses to adequately restore iron status. This is important, given that even in this smaller sample, the two-fold difference in the need for a repeat infusion between the doses represents a significant addition to standard care, with associated costs and no differences in neonatal or child outcome.

Interpretation

The outcomes of this trial suggest that successful treatment of ID can occur with a single 1000mg dose, with no adverse outcomes for antenatal progression, neonatal or child outcomes. This represents an effective treatment modality to shield from the detrimental short- and potential long-term impacts of ID and IDA. Further, adequate iron stores have the potential to positively impact maternal mental health during pregnancy and post-partum; maternal mental health outcomes collected during this trial will be the subject of a subsequent article. Further studies will help to optimise IVI dose, which may be particularly relevant to those countries where 1000mg is not currently routinely used.

Conclusions

Low dose (500mg) intravenous FCM treatment was not equivalent to 1000mg within a 5% margin for successful correction of ID in pregnancy. A single 1000mg does represents an efficient and effective method to clinically manage ID and IDA in pregnancy. A lower dose approach requires ongoing monitoring to ensure adequate iron stores are reached and sustained. Both doses had no adverse impact on neonatal or child outcomes.

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Author Contributions

BF, NAH, GD, and KOS planned the study design. BF, PP, NA, and RC contributed to the collection of data. TLK and NAH performed the data analyses. BF wrote the first draft of the manuscript, which was revised and critically reviewed by all authors. All authors approved the final version.

Competing interests

BF has received financial support to give lectures, undertake research, attend scientific advisory boards, and undertake consultancies for the New South Wales Department of Health, South Australia Department of Health, Australian Red Cross Blood Service, Australian National Blood Authority, Vifor Pharma Ltd., Switzerland, Pharmacosmos A/S Denmark, Pfizer Australia and CSL Behring Australia. KOS, PP, RC, NA, TLK, GD, and NAH have no conflict of interest to declare.

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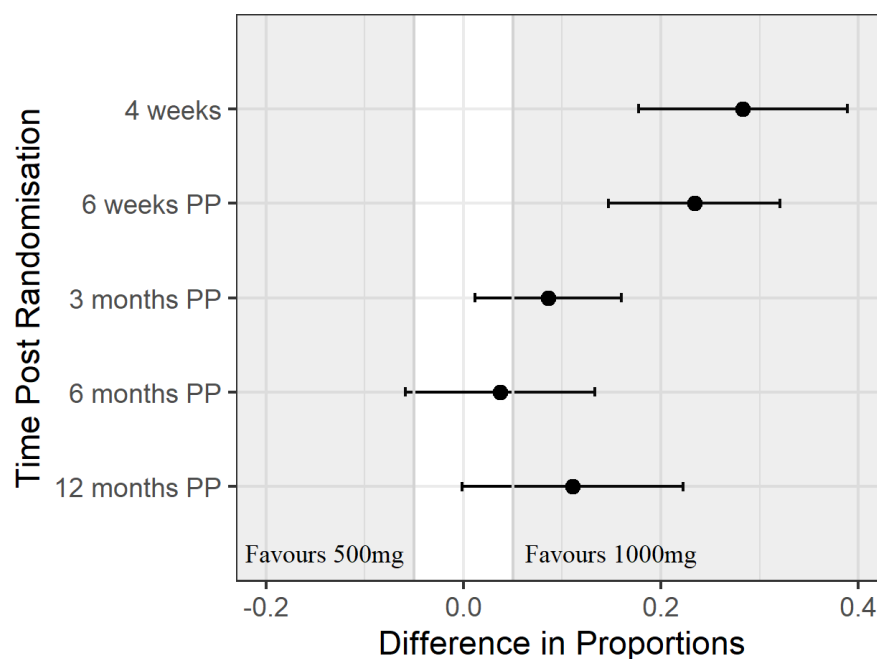
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Figure1_Flowchart_BJOG_final.docx available at <https://authorea.com/users/491742/articles/574617-testing-equivalence-of-two-doses-of-intravenous-iron-to-treat-iron-deficiency-in-pregnancy-a-randomised-controlled-trial>



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Table1_Patient Characteristics.docx available at <https://authorea.com/users/491742/articles/574617-testing-equivalence-of-two-doses-of-intravenous-iron-to-treat-iron-deficiency-in-pregnancy-a-randomised-controlled-trial>

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Table2_primary_outcome.docx available at <https://authorea.com/users/491742/articles/574617-testing-equivalence-of-two-doses-of-intravenous-iron-to-treat-iron-deficiency-in-pregnancy-a-randomised-controlled-trial>

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Table3_secondary_outcome.docx available at <https://authorea.com/users/491742/articles/574617-testing-equivalence-of-two-doses-of-intravenous-iron-to-treat-iron-deficiency-in-pregnancy-a-randomised-controlled-trial>