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RANDOMISED CONTROLLED TRIAL

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 the 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 1000 mg (n = 126) of intravenous ferric carboxymaltose in the second or third trimester.

Main outcome measures: The proportion of participants requiring additional intravenous iron (500 mg) to achieve and maintain ferritin >30 microg/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 time point. 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 [CI] 0.177–0.389). Overall, participants in the 500-mg arm received twice the repeat infusion rate (0.81 [SD = 0.824] versus 0.40 [SD = 0.69], rate ratio 2.05, 95% CI 1.45–2.91).

Conclusions: Administration of 1000 mg 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.

KEYWORDS
antenatal care, haematology: anaemia, medical disorders in pregnancy, obstetric haemorrhage, randomised controlled trials, risk management

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1 | INTRODUCTION

Iron deficiency (ID) is the most common nutritional disorder worldwide, listed on the World Health Organization (WHO) top five 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 birthweight, perinatal death, low Apgar scores, neonatal infection, postnatal ID and impaired cognitive development.[4,7,9,12] In recognition of these adverse outcomes, WHO has targetted a 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 the first-line treatment. Intravenous iron (IVI) is recommended when women are non-responsive, non-tolerant or non-compliant with 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 400 to 1000 mg, 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 geographical, cultural and social barriers.[4,25] Clinicians lack high quality data on the optimal dose to improve and sustain iron status adequately, and to provide sufficient protection against adverse obstetric, neonatal or mental health sequelae. We therefore conducted an RCT comparing two doses of IVI (500 and 1000 mg) using an equivalence design.

2 | 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 IDA 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.

2.1 | Patients

Pregnant women aged over 18 years in the second or third trimester with ID, defined as serum ferritin <15 microg/ml, or serum ferritin <50 microg/ml and TSAT <20% with elevated CRP, were eligible. Participants were excluded if they had untreated B12 or folate deficiencies, known hypersensitivity to FCM, haemoglobin >130 g/l; a serious medical condition, uncontrolled systemic disease or the inability fully to 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.

2.2 | 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 g/l or ≥ 105 g/l. 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]

2.3 | Interventions

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

Iron status was monitored at five study time points: 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 microgl plus transferrin saturation <25% or, if inflammation was present (CRP >7.9 ng/l), ferritin between 30 and 50 microg/l plus a transferrin saturation <20%. If confirmed, ID was treated with a single 500-mg FCM infusion in both groups.

2.4 | Endpoints

The primary endpoint was the proportion of participants requiring additional intravenous FCM to maintain successful

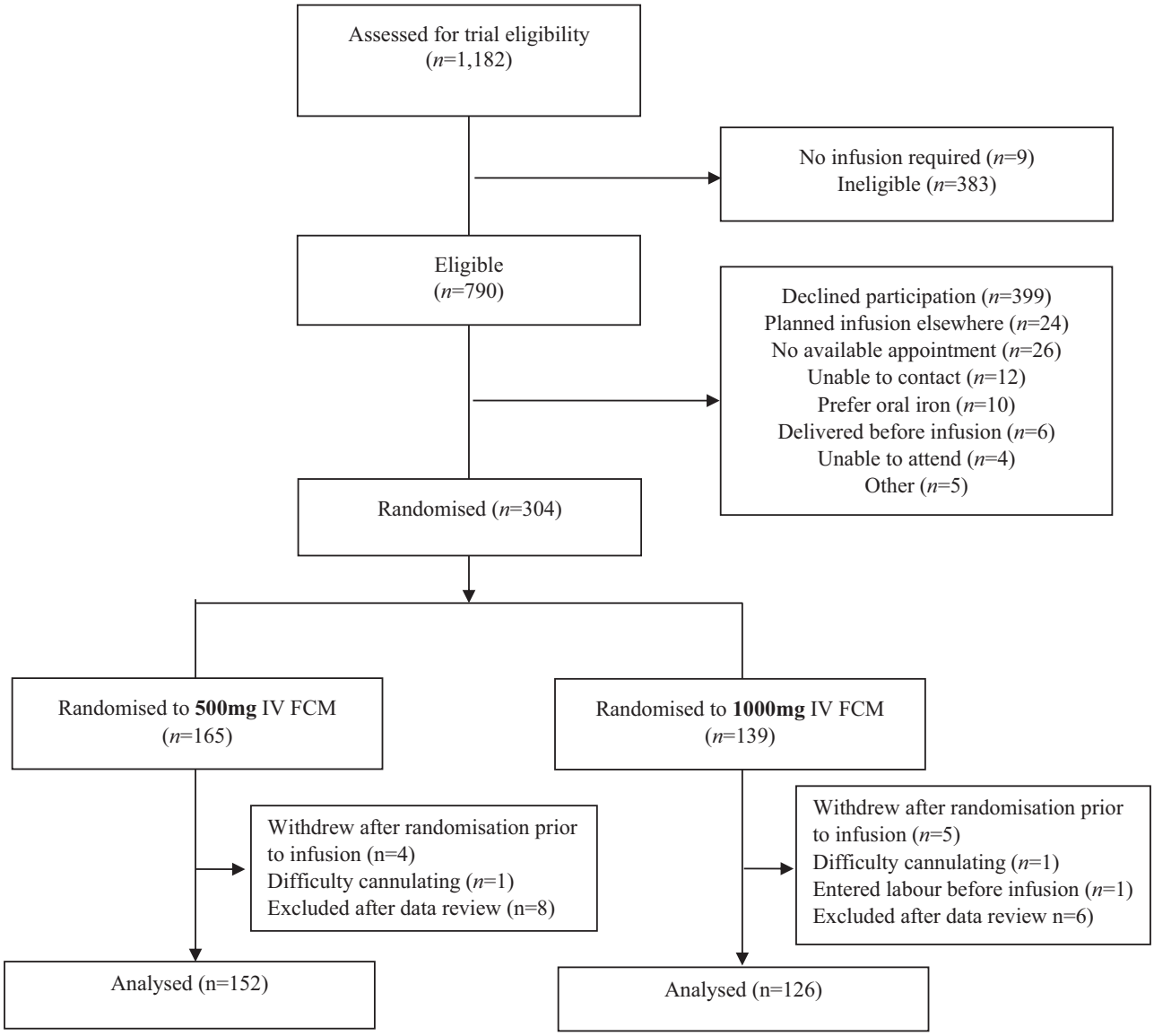

FIGURE 1 Trial flow.

correction of ID, based on the diagnostic criteria. Patients were assessed at the five time points. 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 (birthweight, customised birthweight 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 time points.

2.5 | 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.

2.6 | 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 (Hb < 105 or Hb ≥105) as covariates. Endpoints measured at multiple time points were analysed using repeated measures models with a time point by treatment group interaction. All analyses were performed in SAS v 9.4 (SAS Institute) or R v 4.2.0 (R Foundation for Statistical Computing).

2.6.1 | Primary endpoint

The difference in proportions of participants who required a repeat iron infusion at each time point was analysed using a repeated measures model with generalised estimating equations (GEEs) and an independent working correlation.

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

2.6.2 | 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 microg/l) and was singly imputed as half the limit of detection (2 microg/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 independent 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% CI.

2.7 | Sensitivity and post-hoc analyses

A number of sensitivity analyses were conducted on the primary outcome, described in Appendix S1. As the intervention was only administered in a clinical setting, a further post-hoc sensitivity analysis was conducted. 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.

3 | RESULTS

Between 26 May 2015 and 14 August 2017, 1182 women were screened for trial eligibility at our antenatal assessment unit. Of a total of 304 women who were randomised, nine participants withdrew prior to the infusion, two did not receive the infusion and one entered labour before the infusion. The remaining 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. The median age of participants in both groups was 27 (interquartile range [IQR] 23–31 in the 500-mg group and IQR 22–30 in the 1000-mg group). Median body mass index was 26 (IQR 22–32) and 27 (IQR 23–33) in the 500-mg and 1000-mg groups, respectively. Participants were enrolled in 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.

Equivalence between the two doses at a margin of 5% was not demonstrated at any time point (Table 2, Figure S1). More participants assigned to 500 mg IVI required repeat infusions at 4 weeks post-infusion compared with those assigned to 1000 mg IVI (26/73 [36%] versus 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 decreased but the 90% CI did not lie within the −0.05 to 0.05 interval, therefore equivalence was not achieved within a 5% margin (15/88 [17%] versus 9/67 [13%] at 6 months postpartum; estimated difference in proportions 0.037, 90% CI −0.059 to 0.133). The proportion of participants requiring a repeat infusion increased over time in the 1000-mg IVI group from 5/67 (8%) at 4 weeks post-infusion to 14/70 (20%) at 12 months postpartum.

Equivalence was not achieved in any of the sensitivity analyses of the primary outcome (Tables S1 and S2). The proportion of participants who required a repeat infusion at any time during follow-up was also not equivalent (83/152 [55%] versus 34/126 [27%], estimated difference in proportions 0.288, 90% CI 0.191–0.384) (Table S1). In the ≥105 g/L Hb stratification group, 52/131 (40%) participants required a repeat infusion at any time point, compared with 65/147 (44%) participants in the <105 g/L Hb stratification group (estimated difference in proportions, −0.016, 90% CI −0.112 to 0.081).

Compared with participants assigned to 1000 mg IVI, participants in the 500-mg IVI group received more than twice the repeat infusion rate prior to delivery, after delivery and overall (0.81 [0.84] versus 0.40 [SD = 0.69], rate ratio [RR] 2.05, 95% CI 1.45–2.91; $P < 0.001$) (Table 3).

Participants who received 1000 mg IVI had significantly higher ferritin levels up to 6 months postpartum, compared with those receiving 500 mg IVI (Table 3). Similarly, serum iron and transferrin saturation were higher in participants who received 1000 mg IVI than those who received 500 mg IVI at 4 weeks post-infusion, whereas transferrin was lower

TABLE 1 Characteristics of study participants of the two groups at baseline

	500 mg (*n* = 152)	1000 mg (*n* = 126)
Age, median (IQR)	27 (23–31)	27 (22–30)
Body mass index, median (IQR)	26 (22–32)	27 (23–33)
Pregnant with twins	2 (1%)	1 (1%)
Anaemia, *n* (%)	70 (46%)	66 (52%)
Education, years, median (IQR) (*n*)	13 (12–15) (*n* = 143)	13 (12–15) (*n* = 117)
Income, *n* (%)[a]		
<AUD $40,00	39 (26%)	33 (26%)
AUD $40,000–60,000	37 (24%)	31 (25%)
AUD $60,000–80,000	18 (12%)	25 (20%)
AUD $80,000–120,000	32 (21%)	20 (16%)
>AUD $120,000	13 (9%)	5 (4%)
Unknown	13 (9%)	12 (10%)
Gestational age at screening, median (IQR)		
Days	231 (210–246)	227 (210–244)
Weeks	32.9 (30.0–35.1)	32.4 (30.0–34.8)
Gestational age at first infusion, median (IQR)		
Days	241 (222–255)	235 (222–253)
Weeks	34.4 (31.7–36.5)	33.6 (31.6–36.1)
Blood parameters, mean (SD) (*n*) or median (IQR) (*n*)		
Haemoglobin[b] g/L	106 (9) (*n* = 152)	106 (10) (*n* = 126)
Ferritin microg/L	6.0 (4.0–8.0) (*n* = 152)	6.0 (4.0–9.0) (*n* = 126)
Iron micromol/L	7 (5–10) (*n* = 143)	7 (5–10) (*n* = 119)
Transferrin g/L	4.3 (4.0–5.0) (*n* = 143)	4.5 (4.1–5.0) (*n* = 119)
Transferrin saturation, (%)	6 (5–10) (*n* = 143)	6 (4–9) (*n* = 119)
MCH	28 (26–30) (*n* = 116)	28 (26–29) (*n* = 90)
Folate (serum), nmol/L	28 (21–45) (*n* = 116)	27 (18–41) (*n* = 106)
B12 (serum), pmol/L	198 (162–247) (*n* = 149)	202 (170–244) (*n* = 123)
B12 (active), pmol/L	51 (37–65) (*n* = 115)	49 (32–66) (*n* = 91)
CRP, ng/L	5.7 (2.8–11.0) (*n* = 131)	5.0 (2.3–10.0) (*n* = 113)
Supplements taken in pregnancy, *n* (%)[a]		
None	27 (18%)	18 (14%)
Iron only	15 (10%)	10 (8%)
Iron + pregnancy multivitamin	16 (11%)	15 (12%)
Pregnancy multivitamin (no iron)	55 (36%)	44 (35%)
Other supplements (no iron)	18 (12%)	19 (15%)
Unknown	21 (14%)	20 (16%)

[a]May not add up to 100% due to rounding.
[b]Stratification variable.

(Table 3). Importantly, transferrin saturations remained within normal limits in both groups, safeguarding the fetus from unnecessary transplacental iron transfer. 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 1000 mg iron (dizziness *n* = 2, hypotension *n* = 1, nausea *n* = 1, chest tightness *n* = 1) and 3/150 participants (2%) who received 500 mg 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.

Preterm premature rupture of membranes (PPROM) occurred in 6/121 participants in the 1000-mg arm only. The likelihood of other maternal complications did not differ between participants who received 500 mg and those who

TABLE 2 Primary outcome: The proportion of women requiring a repeat infusion at each time point, *n/N* (%), and estimated difference in proportions between groups (90% CI)

Time period	500 mg (*n* = 152)	1000 mg (*n* = 126)	Estimated difference in proportions, 500–1000 mg (90% CI)
4 weeks post-randomisation	26/73 (36%)	5/67 (8%)	0.283 (0.177–0.389)
6 weeks postpartum	39/118 (33%)	9/83 (11%)	0.234 (0.147–0.321)
3 months postpartum	15/98 (15%)	5/65 (8%)	0.086 (0.012–0.160)
6 months postpartum	15/88 (17%)	9/67 (13%)	0.037 (−0.059 to 0.133)
12 months postpartum	27/90 (30%)	14/70 (20%)	0.111 (−0.001 to 0.222)

received 1000 mg IVI (Table 3). Similarly, no differences were found in the length of gestation, neonatal outcomes or child neurodevelopment at 12 months between the two doses (Table 3).

A post-hoc analysis of haemoglobin levels indicated these were significantly higher in participants in the 1000-mg IVI group than the 500-mg IVI group 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 500- and 1000-mg IVI iron groups. No haemoconcentration occurred in the participants during pregnancy, with minimum and maximum Hb levels during follow-up of 81–167 g/L in the low dose and 99–170 g/L in the high dose arms. There were 6/140 (4%) (minimum–maximum ferritin, 4–434) and 12/116 (10%) (minimum–maximum ferritin, 6–581) participants who experienced hyperferritinaemia during follow-up in the low and high dose arms, respectively. The ferritin value of 581 was measured 2 weeks after infusion and lay within commonly observed peak ferritin concentrations after iron infusion.

3.1 | Main findings

This randomised controlled trial, comparing two pragmatic doses of intravenous iron for treating ID in pregnancy, demonstrated that 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 with 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. Due to the close monitoring provided in this study, women with declining iron stores were able to receive subsequent IVI treatment. Given the higher rate of persistent ID observed in the low dose arm, we would suggest that continued monitoring after infusion of 500 g 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 400 to 1000 mg.[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 about whether IVI prescribing practice for women of reproductive age is appropriate and cost-effective.[24] Our data suggest administration of 1000 mg can significantly reduce the need for repeat IVI, thereby improving patient health while reducing clinical load and cost. 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.

Iron deficiency 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 500- and 1000-mg IVI arms, with the exception of PPROM, which occurred only in participants receiving 1000 mg. Although the pathways leading to PPROM 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 PPROM in the current study.[29] However, this must be interpreted with caution given the present study was not powered to examine this outcome.

Pregnancy is 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.[20,30] 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.[31] Although routine in our obstetrics unit, screening for ID is rarely incorporated into routine antenatal care.[32] 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.[16,22,23,33–36]

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TABLE 3 Secondary outcomes

Outcome	Time point	500 mg	1000 mg	Estimate (95% CI)	*P*-value
Rate of repeat infusions,[a] mean (SD) (*n*)		*n* = 152	*n* = 126		
	Prior to delivery	0.37 (0.51) (*n* = 76)	0.14 (0.35) (*n* = 77)	2.58 (1.38–4.82)	0.003
	After delivery	0.64 (0.72) (*n* = 140)	0.31 (0.57) (*n* = 111)	2.10 (1.42–3.10)	<0.001
	Overall	0.81 (0.84) (*n* = 140)	0.40 (0.69) (*n* = 111)	2.05 (1.45–2.91)	<0.001
Iron status, mean (SD) (*n*)					
Ferritin[b] microg/L (half threshold method)	4 weeks	57 (49) (*n* = 69)	147 (100) (*n* = 65)	−90.1 (−115.1 to −65.1)	<0.001
	6 weeks PP	68 (61) (*n* = 115)	115 (76) (*n* = 82)	−53.0 (−71.8 to −34.3)	0.004
	3 months PP	75 (50) (*n* = 97)	96 (66) (*n* = 64)	−25.7 (−43.0 to −8.5)	<0.001
	6 months PP	58 (30) (*n* = 85)	85 (64) (*n* = 61)	−28.6 (−42.1 to −15.2)	<0.001
	12 months PP	58 (52) (*n* = 88)	69 (59) (*n* = 66)	−8.5 (−24.8 to 7.8)	0.31
Transferrin saturation,[b] %	4 weeks	13 (6) (*n* = 67)	20 (8) (*n* = 62)	−6.4 (−8.7 to −4.1)	<0.001
	6 weeks PP	20 (10) (*n* = 114)	22 (9) (*n* = 81)	−1.2 (−4.0 to 1.6)	0.40
	3 months PP	22 (10) (*n* = 96)	23 (9) (*n* = 64)	−1.3 (−4.0 to 1.4)	0.34
	6 months PP	20 (9) (*n* = 84)	21 (9) (*n* = 58)	0.1 (−3.1 to 3.2)	0.96
	12 months PP	20.98 (9.06) (*n* = 86)	19.72 (9.64) (*n* = 64)	1.78 (−1.36 to 4.93)	0.27
Antenatal and delivery, *n*/*N* (%)					
Gestational diabetes[c]		23/150 (15%)	27/121 (22%)	0.61 (0.32–1.13)	0.12
Pre-eclampsia[c]		4/150 (3%)	9/122 (7%)	0.33 (0.10–1.10)	0.07
Preterm delivery[c]		5/151 (3%)	7/126 (6%)	0.56 (0.17–1.82)	0.34
Antepartum haemorrhage[d]		5/150 (3%)	9/121 (7%)	0.43 (0.14–1.32)	0.14
Postpartum haemorrhage (EBL >500 ml)[c]		41/150 (27%)	37/124 (30%)	0.87 (0.51–1.48)	0.61
PPROM		0/150 (0%)	6/121 (5%)	—	0.007[e]
Mode of delivery[e]					
Normal vaginal, reference		85/151 (56%)	76/126 (60%)	1.00	
Instrumental vaginal		16/151 (11%)	9/126 (7%)	1.62 (0.67–3.88)	0.28
Emergency caesarean section		18/151 (12%)	13/126 (10%)	1.23 (0.57–2.69)	0.60
Elective caesarean Section		32/151 (21%)	28/126 (22%)	0.98 (0.54–1.79)	0.95
Neonatal outcomes,[f] mean (SD)					
Gestational age at delivery, days		275 (10) (*n* = 151)	275 (9) (*n* = 126)	0.28 (−1.93 to 2.50)	0.80
Birthweight, g		3513 (532) (*n* = 151)	3522 (468) (*n* = 126)	−28.6 (−187.2 to 130.0)	0.72
Birthweight centile		51 (30) (*n* = 151)	52 (29) (*n* = 126)	−1.78 (−8.91 to 5.35)	0.63
Birth length, cm		50 (2) (*n* = 151)	50 (2) (*n* = 124)	−0.17 (−1.52 to 1.17)	0.80
Head circumference, cm		35 (2) (*n* = 151)	35 (2) (*n* = 126)	−0.30 (−1.25 to 0.64)	0.53
Child neurodevelopment,[f] mean (SD) (*n*)	12 months				
Communication		49 (11) (*n* = 77)	51 (10) (*n* = 53)	−1.36 (−5.03 to 2.32)	0.47
Gross motor		45 (16) (*n* = 75)	46 (17.3) (*n* = 53)	−1.67 (−7.56 to 4.21)	0.58
Fine motor		50 (10) (*n* = 77)	51 (11) (*n* = 53)	−0.44 (−4.18 to 3.30)	0.82
Problem solving		43 (14) (*n* = 76)	47 (13) (*n* = 53)	−3.67 (−8.31 to 0.97)	0.12

Abbreviations: MD, mean difference; OR, odds ratio; RM, repeated measures; RR, rate ratio.

[a]RM Poisson regression: estimate is RR for 500/1000 mg adjusted for stratification.

[b]RM linear mixed models: estimate is MD for 500–1000 mg adjusted for baseline and stratification.

[c]Logistic regression: estimate is OR for outcome for 500/1000 mg adjusted for stratification.

[d]Fisher's exact test.

[e]Multinomial logistic regression: estimate is OR for category versus reference for 500/1000 mg adjusted for stratification.

[f]Linear regression: estimate is MD for 500–1000 mg adjusted for stratification.

3.2 | Strengths and limitations

The strengths of this study include the blinding of clinician, healthcare 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-week 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.

3.3 | Interpretation

The outcomes of this trial suggest that successful treatment of ID can occur with a single 1000- mg 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 have a positive impact on maternal mental health during pregnancy and postpartum; 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 1000 mg is not currently routinely used.

4 | CONCLUSIONS

Low dose (500 mg) intravenous FCM treatment was not equivalent to 1000 mg within a 5% margin for successful correction of ID in pregnancy. A single 1000 mg does represents an efficient and effective method to manage ID and IDA clinically in pregnancy. A lower dose approach requires ongoing monitoring to ensure adequate iron stores are reached and sustained. Neither doses had any adverse impact on neonatal or child outcomes.

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 article, which was revised and critically reviewed by all authors. All authors approved the final version.

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CONFLICT OF INTERESTS

BF has received financial support to give lectures, and attend scientific advisory boards for Vifor Pharma Ltd., Switzerland, Compai Pharma, Malaysia, and Pfizer Australia. KOS, PP, RC, NA, TLK, GD and NAH have no conflict of interests to declare. Completed disclosure of interest forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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