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Iron deficiency in pregnancy: fetal Doppler changes before anaemia and ferric carboxymaltose versus iron sucrose in primary care

A prospective comparative cohort study from Uzbekistan

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WHAT IS ALREADY KNOWN	WHAT THIS STUDY ADDS	HOW THIS MIGHT AFFECT PRACTICE
Haemoglobin-only antenatal screening identifies iron deficiency only after stores and transport are exhausted. Intravenous iron corrects anaemia faster than oral iron, but head-to-head evidence between intravenous formulations delivered within primary health care (PHC) in Central Asia is scarce.	Fetal haemodynamic change (cerebroplacental ratio 0.98 vs 1.33) is already detectable in prelatent iron deficiency with normal haemoglobin. In moderate anaemia, hepcidin remained coupled to iron stores while erythropoietin was uncoupled from haemoglobin, identifying substrate, not signalling, as the bottleneck. Single-visit ferric carboxymaltose was associated with deeper and more durable repletion than iron sucrose and with half the rate of postpartum haemorrhage >500 mL.	Ferritin and transferrin saturation (with hepcidin where available) should complement haemoglobin at booking; a cerebroplacental ratio <1.0 can serve as a trigger to escalate from prophylactic to therapeutic iron. A PHC day-care pathway with 1–2 ferric carboxymaltose infusions is feasible and resource-saving.

ABSTRACT

Background: Antenatal care relies on haemoglobin (Hb) to detect iron deficiency (ID), although Hb falls only after iron stores and transport are depleted. Whether fetal haemodynamics change before anaemia, and which intravenous iron works best in primary health care (PHC), is unclear.

Methods: Prospective cohort study in PHC facilities in three Uzbek regions (2021–2025). Women were staged by ferritin, transferrin saturation (TSAT) and hepcidin and underwent fetal–placental Doppler. Women with moderate iron-deficiency anaemia (IDA) in the second–third trimester unresponsive to oral iron received ferric carboxymaltose (FCM; n = 163) or iron sucrose (IS; n = 167); 30 non-anaemic women were controls. Outcomes were Hb and iron indices at 4 weeks and 2 months, tolerability and obstetric outcomes.

Results: Of 430 screened women, 43 had prelatent ID with normal Hb; their cerebroplacental ratio was lower than in controls (0.98 ± 0.12 vs 1.33 ± 0.10; p < 0.001). In moderate IDA, hepcidin correlated with ferritin (ρ = 0.53), whereas erythropoietin was unrelated to Hb (ρ = −0.08). The FCM group started with lower ferritin and TSAT. At 4 weeks, Hb was higher with FCM (118.1 vs 107.8 g/L; difference 10.3, 95% CI 9.4–11.2). At 2 months, ferritin was 42.6 vs 18.3 µg/L. FCM needed fewer infusions (1.3 vs 5.4) and caused fewer adverse events (8.6% vs 17.4%). Postpartum haemorrhage >500 mL (12.3% vs 25.7%; risk ratio [RR] 0.48, 95% CI 0.29–0.77) and day-3 Hb <100 g/L (8.0% vs 28.1%; RR 0.28, 0.16–0.50) were less frequent with FCM.

Conclusions: In PHC, the cerebroplacental ratio was already reduced in prelatent ID, before anaemia. Single-visit FCM for moderate IDA was associated with faster, more durable repletion and fewer postpartum complications than IS. These non-randomised findings need confirmation in a randomised trial.

Keywords: iron-deficiency anaemia; pregnancy; hepcidin; ferritin; transferrin saturation; cerebroplacental ratio; ferric carboxymaltose; iron sucrose; primary health care; Uzbekistan

1 INTRODUCTION

Anaemia affects roughly one in three pregnant women worldwide, and iron deficiency is its leading cause [1,2]. Severe anaemia in pregnancy and the postpartum period is independently associated with maternal death, and both low and high haemoglobin concentrations are associated with adverse maternal and neonatal outcomes [3,4]. International guidance therefore emphasises early recognition and correction of iron deficiency, with intravenous iron recommended from the second trimester when oral iron fails or time is short [5–7].

In practice, however, most antenatal programmes—including the primary health care (PHC) network in Uzbekistan—continue to screen with haemoglobin alone. Haemoglobin is a late and insensitive marker: it falls only after iron stores (ferritin) and iron transport (transferrin saturation, TSAT) have been exhausted, and physiological haemodilution further blurs its interpretation [5,8]. A substantial proportion of non-anaemic pregnant women are already iron-deficient, and ferritin testing in antenatal care remains inconsistent even in high-resource settings [9,10]. Hepcidin, the master regulator of iron absorption and recycling, falls physiologically in pregnancy and may help identify iron deficiency before anaemia [11,12], yet its place within a primary-care diagnostic pathway has not been defined.

Iron is prioritised to the fetus, but the fetal brain is vulnerable when maternal supply is insufficient [13,14]. The cerebroplacental ratio (CPR) is a sensitive Doppler marker of fetal haemodynamic redistribution that reflects placental reserve independently of fetal size [15,16]. Whether CPR changes across the stages of maternal iron deficiency—particularly before anaemia appears—has not been examined.

Finally, when moderate anaemia does develop, the choice of intravenous preparation matters for a PHC system. Ferric carboxymaltose (FCM) allows replacement in one or two short infusions, whereas iron sucrose (IS) requires repeated visits. Randomised trials and meta-analyses support the haematological superiority of intravenous over oral iron in pregnancy [17–20], and recent large trials in Nigeria, Malawi and India found that a single FCM infusion corrected iron deficiency better than oral iron, although effects on overall anaemia and clinical outcomes varied [21–23]. Head-to-head data comparing intravenous formulations within primary care, with regulatory, Doppler and obstetric endpoints, are limited, and none come from Central Asia.

We therefore aimed to (i) characterise the store–transport–regulation phenotype of iron deficiency across its stages in pregnant women attending PHC; (ii) determine whether fetal–placental haemodynamics are altered before anaemia; and (iii) compare single-visit FCM with IS for moderate iron-deficiency anaemia (IDA) on haematological, regulatory, clinical and obstetric outcomes.

2 METHODS

2.1 Design, setting and reporting

This prospective comparative cohort study was nested in a mixed-methods programme on antenatal care in PHC conducted in 2021–2025 in three regions of Uzbekistan that differ in socio-demographic profile and health infrastructure: Tashkent city, the Tashkent region (Chinaz, Bekabad and Akhangaran districts) and the Surkhandarya region (Termez city and the Denau, Sherabad and Kumkurgan districts). Facilities were selected by two-stage cluster sampling (eight geographical clusters). All diagnostic work-up, treatment and follow-up took place in PHC outpatient clinics and PHC day-care units, without referral to specialised inpatient services. The study is reported in accordance with the STROBE statement. Because the treatment comparison was observational, the study was not registered in a clinical-trial registry.

2.2 Participants and iron-status staging

Pregnant women attending PHC underwent a structured clinical examination, an iron-deficiency self-assessment questionnaire (A. Arsenyeva's self-test "How well do I know iron deficiency?", adapted for pregnancy and administered through the soglomona.uz online platform), a full blood count and iron-status testing. Women with C-reactive protein (CRP) >10 mg/L (n = 18) were excluded from biomarker analyses because ferritin and hepcidin behave as acute-phase reactants. Anaemia was defined by the WHO 2024 cut-offs: Hb <110 g/L in the first trimester, <105 g/L in the second and <110 g/L in the third [2]. Severity was graded by the national classification of Uzbekistan (mild 90–109 g/L, moderate 70–89 g/L, severe <70 g/L) [24]; WHO grades 70–99 g/L as moderate anaemia [2]. Iron-deficiency stages were defined by laboratory criteria alone (Table 1); Doppler indices were not part of the staging and were analysed as outcomes. The study flow is shown in Figure 1.

The therapeutic cohort comprised women at 13–38 weeks of gestation with moderate (grade II) IDA by the national classification (Hb 70–89 g/L), ferritin <30 µg/L with raised total iron-binding capacity (TIBC) and TSAT <20%, who had not responded to oral prophylaxis with 60 mg/day of elemental iron. Exclusion criteria were first trimester, severe anaemia (Hb <70 g/L) requiring hospitalisation, active infection or malignancy, contraindications to intravenous iron and participation in another trial within 6 months. Thirty pregnant women of similar age and gestation with normal haematological and iron indices formed the control group. The therapeutic cohort comprised women from the same PHC facilities whose anaemia progressed to moderate IDA

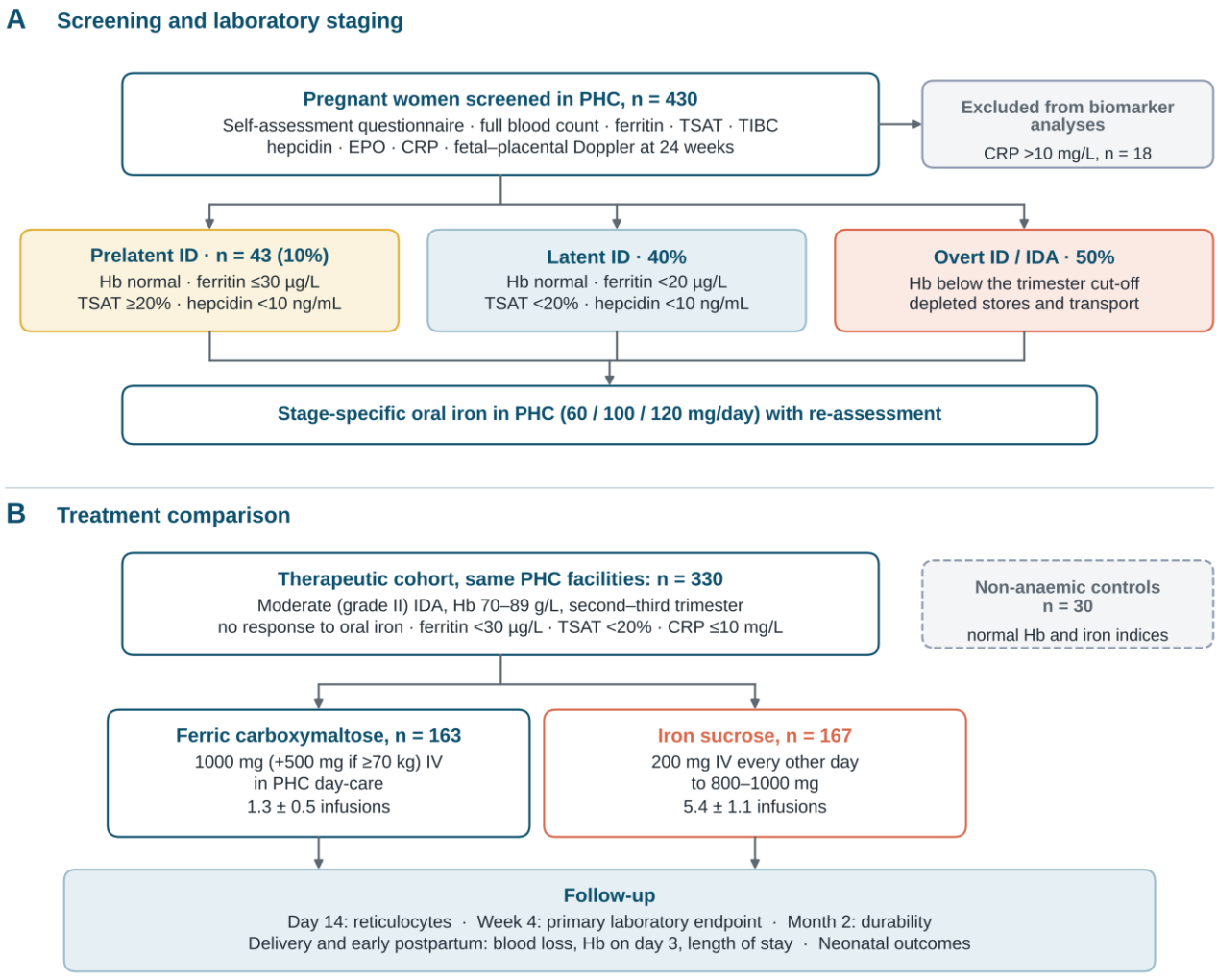
despite oral iron, including non-responders identified through the screening sample. Treatment was not randomised: women received FCM or IS as prescribed in routine care at the participating facilities.

Table 1. Operational staging of iron deficiency in pregnancy used in this study and the corresponding PHC action.

Stage	Hb, g/L	Ferritin, µg/L	TSAT, %	Hepcidin, ng/mL	PHC action in the study
Iron replete	≥110†	>30	20–45	≥10	Routine prophylaxis
Prelatent ID	≥110†	≤30	—	<10	Oral iron 60 mg/day; re-test
Latent ID	≥110†	<20	<20	<10	Oral iron 100 mg/day; Doppler surveillance
Overt ID / mild IDA	90–109†	<15–20	<20	<10	Oral iron 120 mg/day; re-assess at 2 weeks
Moderate IDA (grade II)	70–89	<30	<20	<10	IV iron in PHC day-care (FCM or IS)

Anaemia was defined by the WHO 2024 cut-offs: Hb <110 g/L in the first, <105 g/L in the second and <110 g/L in the third trimester [2]. †In the second trimester the cut-off is 105 g/L, so mild IDA spans 90–104 g/L. Severity grades follow the national classification (mild 90–109 g/L, moderate 70–89 g/L) [24]; WHO grades 70–99 g/L as moderate anaemia [2]. Staging used laboratory criteria only; TSAT was recorded but was not a criterion for the prelatent stage. Most women with moderate IDA had ferritin <15 µg/L (Table 3). FCM, ferric carboxymaltose; ID, iron deficiency; IDA, iron-deficiency anaemia; IS, iron sucrose; IV, intravenous; PHC, primary health care; TSAT, transferrin saturation.

Figure 1. Study flow. (A) Screening cohort and laboratory staging of iron deficiency. (B) Therapeutic cohort and treatment comparison.



Stage percentages refer to the 430 screened women. CRP, C-reactive protein; EPO, erythropoietin; ID, iron deficiency; IDA, iron-deficiency anaemia; IV, intravenous; PHC, primary health care; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

2.3 Interventions

FCM was infused in 250 mL of 0.9% saline in a PHC day-care unit at 1000 mg, followed by a second dose of 500 mg after 6 days in women weighing ≥70 kg (maximum cumulative dose 1500 mg). IS was administered intravenously at 200 mg every other day up to a cumulative dose of 800–1000 mg over 7–10 days. Local, autonomic, gastrointestinal and allergy-like reactions were recorded during and after each infusion.

2.4 Laboratory and Doppler assessment

Venous blood was drawn in the fasting state. Haematological indices and reticulocytes were measured on a Mindray BC-5150 analyser; serum iron (ferrozine method) and TIBC on a Rayto RT-9200 analyser; ferritin (ELISA, Stat Fax 4200); hepcidin-25 (DRG ELISA); EPO (Elabscience ELISA); and CRP by turbidimetry (BioSystems BA-400). TSAT was calculated as serum iron/TIBC × 100. Ferritin samples were stored at −20 °C and assayed in triplicate. Laboratory assessments were performed at baseline, day 14 (reticulocytes), week 4 and month 2.

Doppler examinations were performed at 24–28 weeks (Mindray DC-70) by measuring the pulsatility index (PI) and resistance index (RI) of the uterine arteries and the PI of the umbilical artery and fetal middle cerebral artery; CPR was calculated as PI_{MCA}/PI_{UA}. Measurements followed ISUOG and FIGO guidance [16,25]. Uterine artery PI >1.42 and/or RI >0.75 defined abnormal uteroplacental flow. A CPR <1.0 was taken to indicate cerebral redistribution; this single fixed cut-off was used throughout, and gestation-specific centiles were not applied. Each woman was examined once, at 24–28 weeks. Because about 60% of the therapeutic cohort were enrolled at 13–20 weeks (Table 2), in most women with moderate IDA the scan took place after the first infusion. Doppler findings were used descriptively and did not influence group assignment.

2.5 Outcomes

The primary laboratory endpoint was Hb at 4 weeks. Secondary endpoints were ferritin, TSAT, hepcidin, EPO, MCV and MCH at 4 weeks and 2 months; attainment of predefined targets at 4 weeks (Hb ≥110 g/L, ferritin ≥30 µg/L, normalisation of hepcidin to the non-anaemic range, EPO ≤45 mIU/mL); anaemia symptoms; adverse events and treatment discontinuation; mode of delivery, labour induction, blood loss and postpartum haemorrhage (>500 mL); Hb on postpartum day 3; repeat postpartum iron; length of postpartum stay; birthweight, fetal growth restriction and neonatal transfer to intensive or special care.

2.6 Statistical analysis

Analyses were performed in IBM SPSS Statistics 25.0. Normality was assessed with the Shapiro–Wilk test. Continuous variables are reported as mean ± SD and compared with Welch's t-test between groups and the paired t-test within groups; ferritin was right-skewed after treatment, but with more than 160 women per group Welch's test of means is robust to this skewness. Three-group comparisons used ANOVA or the Kruskal–Wallis test. Categorical variables were compared with Pearson's χ^2 or Fisher's exact test. Spearman's ρ described correlations between laboratory and Doppler variables. Between-group differences are expressed as mean differences (MD) with Welch 95% confidence intervals (CI) and Cohen's *d*, risk ratios (RR) with log-method 95% CI, absolute risk differences (ARD) and the number needed to treat (NNT). Between-group estimates are unadjusted; their robustness to confounding was examined in sensitivity analyses based on group summary statistics. For continuous 4-week outcomes, estimates adjusted for the baseline value by analysis of covariance were bounded over the plausible range of baseline–follow-up correlations (0 to 1). For binary outcomes, E-values were calculated: the minimum risk ratio by which an unmeasured or unadjusted confounder would have to be associated with both treatment and outcome to explain away the observed effect [26]. Ferritin at 2 months was also compared as a ratio of geometric means under a log-normal distribution. With 163 and 167 women, the study had 83% power at a two-sided α of 0.05 to detect a halving of postpartum haemorrhage >500 mL from 25% to 12.5%. Outcome data were complete for all 330 women at 4 weeks, 2 months and delivery; the three women who discontinued iron sucrose were analysed in their original group. Two-sided $p < 0.05$ was considered significant.

2.7 Ethics

The study conformed to the Declaration of Helsinki (2013) and was approved by the local ethics committee of the Tashkent Medical Academy, now Tashkent State Medical University (protocol No. 11-07/16612, 5 November 2021). All participants gave written informed consent in Uzbek or Russian.

3 RESULTS

3.1 Study population

Of the 430 screened pregnant women, 43 (10%) had prelatent, about 40% latent and about 50% overt iron deficiency (Figure 1A). The therapeutic cohort included 330 women with moderate IDA (163 FCM, 167 IS; Figure 1B); 21 (6.4%) were aged 18–20 years, 209 (63.3%) were aged 21–30, 67 (20.3%) were aged 31–35 and 33

(10.0%) were older than 35 years. Rural residents predominated among women with moderate IDA (69.1% vs 30.9% urban). The two treatment groups were comparable in gestational age, body-mass index, parity, timing of booking, folate use, comorbidity and symptom burden (Table 2), and baseline Hb did not differ significantly (84.3 vs 85.1 g/L; p = 0.057). Haematocrit and red-cell count were, however, slightly lower and MCH slightly higher in the FCM group, and this group also had a deeper iron deficit (Section 3.2). Underweight was twice as frequent in both anaemic groups as in controls (16.0% and 12.6% vs 6.7%), and more than three-quarters of anaemic women reported three or more symptoms at baseline. CRP, leucocyte counts and neutrophil–lymphocyte balance were normal and similar across groups, excluding anaemia of inflammation.

Table 2. Baseline characteristics of the therapeutic cohort and controls.

Characteristic	FCM (n = 163)	IS (n = 167)	Controls (n = 30)	p FCM vs IS
Obstetric profile				
Gestational age 13–20 / 21–24 / 25–38 wk, %	59.5 / 24.5 / 16.0	62.3 / 24.6 / 13.2	60.0 / 23.3 / 16.7	>0.05
≥2 pregnancies, %	76.1	75.4	80.0	>0.05
≥1 previous birth, %	74.2	73.7	76.7	>0.05
≥1 induced abortion / miscarriage, %	22.7 / 16.0	23.4 / 16.8	3.3 / 0.0	>0.05
Booking before 12 weeks, %	66.3	67.7	83.3	>0.05
Folic acid before enrolment, %	75.5	75.4	93.3	>0.05
Body-mass index (WHO), n (%)				
<18.5 kg/m²	26 (16.0)	21 (12.6)	2 (6.7)	>0.05
18.5–24.9 kg/m²	94 (57.7)	99 (59.3)	21 (70.0)	>0.05
25.0–29.9 kg/m²	32 (19.6)	34 (20.4)	6 (20.0)	>0.05
≥30.0 kg/m²	11 (6.7)	13 (7.8)	1 (3.3)	>0.05
Comorbidity, %				
Endocrine disorders	41.1	38.3	6.7	0.606
Gastrointestinal disease	16.6	15.0	3.3	0.691
Chronic genital-tract inflammation	23.9	25.7	10.0	0.702
Family history of anaemia	11.7	10.8	3.3	0.800
Symptoms, %				
≥3 symptoms simultaneously	78.5	79.0	10.0	0.909
Weakness / exertional dyspnoea	72.4 / 58.3	72.5 / 58.7	13.3 / 6.7	>0.05
Dizziness / pica	53.4 / 25.8	54.5 / 26.3	3.3 / 3.3	>0.05
Haematology and inflammation, mean ± SD				
Hb, g/L	84.3 ± 3.9	85.1 ± 3.7	112.6 ± 4.2	0.057
Haematocrit, %	30.7 ± 2.1	31.2 ± 2.3	36.4 ± 1.9	0.040
RBC, ×10¹²/L	3.58 ± 0.42	3.69 ± 0.45	4.12 ± 0.38	0.022
MCV, fL / MCH, pg	82.3 ± 4.7 / 23.5 ± 1.8	83.1 ± 5.1 / 23.1 ± 1.6	88.2 ± 4.3 / 30.4 ± 1.9	0.139 / 0.034
MCHC, g/dL	30.5 ± 1.1	30.6 ± 1.2	34.4 ± 1.3	0.430
CRP, mg/L	2.3 ± 1.4	2.1 ± 1.5	2.2 ± 1.3	0.211
Leucocytes, ×10⁹/L	6.7 ± 1.2	6.5 ± 1.3	6.4 ± 1.1	0.147

All anaemic groups differed from controls for haematological indices (p <0.001). p FCM vs IS: Welch's t-test for continuous and Pearson's χ^2 test for categorical variables. FCM, ferric carboxymaltose; IS, iron sucrose; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cells.

3.2 A substrate-limited, regulation-intact phenotype

Women with moderate IDA had profound depletion of stores and transport: ferritin was 7.2 ± 2.6 and 8.1 ± 2.4 µg/L in the FCM and IS groups versus 53.8 ± 4.5 µg/L in controls, and TSAT was 8.1 ± 1.9% and 8.8 ± 2.1% versus 27.1 ± 3.6% (Table 3). More than 80% had ferritin <15 µg/L. The FCM group started from a deeper deficit: serum iron, ferritin and TSAT were lower and TIBC and EPO higher than in the IS group (all p ≤0.015), and ferritin <10 µg/L was more frequent, although this difference did not reach significance (63.2% vs 53.3%; p = 0.068). Hepcidin did not differ between the groups (p = 0.71). Reticulocytes were low in both groups but higher with FCM (2.8 vs 2.4‰; p <0.001). The deeper deficit would tend to bias iron-repletion outcomes against FCM, whereas the higher reticulocyte count could favour an early Hb response. The between-group estimates reported below are unadjusted and are interpreted with these imbalances in mind (Section 4.4).

Table 3. Iron store, transport and regulatory markers before treatment.

Marker	FCM (n = 163)	IS (n = 167)	Controls (n = 30)	p FCM vs IS	p vs controls
Store and transport compartment					
Serum iron, µmol/L	6.1 ± 0.9	6.4 ± 1.0	14.7 ± 2.2	0.004	<0.001
Ferritin, µg/L	7.2 ± 2.6	8.1 ± 2.4	53.8 ± 4.5	0.001	<0.001
TIBC, µmol/L	75.6 ± 5.4	74.1 ± 5.7	54.3 ± 4.8	0.015	<0.001
TSAT, %	8.1 ± 1.9	8.8 ± 2.1	27.1 ± 3.6	0.002	<0.001
Ferritin distribution, n (%)					
<10 µg/L	103 (63.2)	89 (53.3)	0	0.068	<0.001
10–15 µg/L	46 (28.2)	56 (33.5)	0	0.296	<0.001
16–30 µg/L	14 (8.6)	22 (13.2)	0	0.182	<0.001
>30 µg/L	0	0	30 (100)	—	<0.001
Regulatory axis					
Hepcidin-25, ng/mL	7.1 ± 2.3	7.2 ± 2.5	20.6 ± 3.2	0.706	<0.001
Erythropoietin, mIU/mL	57.3 ± 8.9	54.6 ± 8.3	41.8 ± 6.2	0.005	<0.001
Reticulocytes, ‰	2.8 ± 0.3	2.4 ± 0.2	14.6 ± 0.6	<0.001	<0.001

Values are mean ± SD unless stated otherwise. Controls were selected for normal haematological and iron indices, which narrows the dispersion of these markers. p FCM vs IS: Welch's t-test or Pearson's χ^2 test; p vs controls: ANOVA or χ^2 test. TIBC, total iron-binding capacity; TSAT, transferrin saturation.

The correlation structure (Table 4) showed that the regulatory feedback loop was preserved. Hepcidin tracked iron stores (ρ = 0.53 with ferritin; ρ = 0.41 with TSAT) and was inversely related to Hb (ρ = −0.44), the strongest correlate of Hb in the matrix. TSAT, the marker of iron available to the erythron, correlated more strongly with Hb (ρ = 0.38) than ferritin did (ρ = 0.29). In contrast, EPO was elevated but unrelated to Hb (ρ = −0.08), TSAT or reticulocytes and only weakly related to ferritin (ρ = −0.12), a pattern of *functional hyporegeneration* in which the erythropoietic signal is present but cannot be executed for lack of substrate. Together with normal CRP, the tight hepcidin–ferritin coupling argues against an inflammatory component and identifies iron substrate, rather than its regulation, as the rate-limiting step.

Table 4. Spearman correlation matrix of erythroid and iron-regulatory markers in moderate iron-deficiency anaemia (n = 330), shaded by direction and strength.

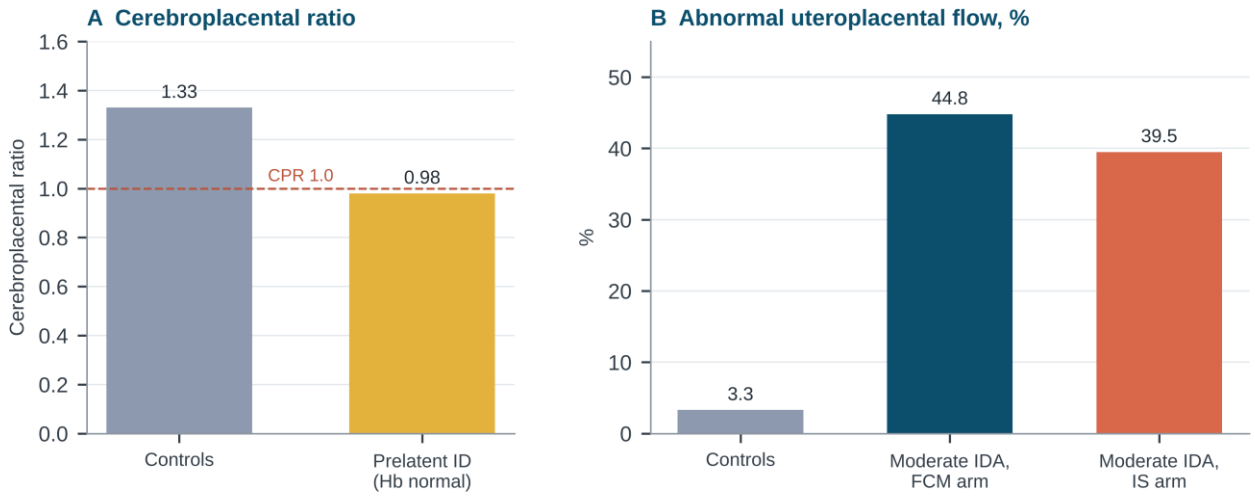
	Hb	Ferritin	Hepcidin	EPO	TSAT	Reticulocytes
Hb	—	**0.29****	**−0.44****	−0.08	**0.38****	**0.39****
Ferritin	**0.29****	—	**0.53****	−0.12*	**0.47****	0.09
Hepcidin	**−0.44****	**0.53****	—	−0.10	**0.41****	−0.04
EPO	−0.08	−0.12*	−0.10	—	−0.07	0.03
TSAT	**0.38****	**0.47****	**0.41****	−0.07	—	**0.24****
Reticulocytes	**0.39****	0.09	−0.04	0.03	**0.24****	—

Teal, positive and coral, negative correlations; colour intensity is proportional to |ρ|. *p <0.05; **p <0.01 (n = 330). EPO, erythropoietin; TSAT, transferrin saturation.

3.3 Fetal–placental haemodynamics change before anaemia

In women with prelatent iron deficiency and normal Hb (n = 43), umbilical artery PI at 24 weeks was not raised (1.02 vs 1.20 in controls), whereas middle cerebral artery PI was lower (1.00 vs 1.60), so CPR was already reduced (0.98 ± 0.12 vs 1.33 ± 0.10; MD −0.35; p <0.001). This pattern indicates early cerebral redistribution without a rise in placental resistance (Figure 2A). Because the prelatent stage was defined by laboratory criteria alone, this difference does not follow from the staging definition. In moderate IDA, examined at 24–28 weeks and thus after the first infusion in most women (Section 2.4), the signal extended to the maternal side: uterine artery PI (1.44 ± 0.17 and 1.41 ± 0.16 vs 1.18 ± 0.14) and RI (0.76 ± 0.05 and 0.74 ± 0.06 vs 0.66 ± 0.04) were higher than in controls (both p <0.001), and abnormal uteroplacental flow was present in 139 of 330 women (42.1%) versus 1 of 30 controls (3.3%) (Figure 2B). Doppler indices tracked iron status: uterine artery PI correlated inversely with Hb (ρ = −0.33) and ferritin (ρ = −0.35), RI with TSAT (ρ = −0.31) and CPR with hepcidin (ρ = −0.26).

Figure 2. Fetal–placental haemodynamics across the iron-deficiency continuum. (A) Cerebroplacental ratio in controls and in prelatent iron deficiency; values <1.0 indicate cerebral redistribution. (B) Proportion with abnormal uteroplacental flow (uterine artery PI >1.42 and/or RI >0.75).



Panel A: prelatent iron deficiency vs controls at 24 weeks. Panel B: moderate IDA groups at 24–28 weeks (after the first infusion in most women; Section 2.4). FCM, ferric carboxymaltose; ID, iron deficiency; IDA, iron-deficiency anaemia; IS, iron sucrose.

3.4 Haematological and regulatory recovery

Both regimens raised Hb and iron indices, and recovery was faster, larger and more durable with FCM in every compartment (Figure 3; Table 5). At 4 weeks, Hb rose by 33.8 g/L with FCM versus 22.7 g/L with IS, giving a between-group difference of 10.3 g/L (95% CI 9.4–11.2; d = 2.48). Ferritin reached 132.4 µg/L versus 86.6 µg/L (MD 45.8 µg/L), and TSAT 25.8% versus 15.9%, although FCM recipients had started from lower ferritin and TSAT. Because the FCM group started lower on all three markers, adjustment for baseline values can only widen these differences: for any baseline–follow-up correlation between 0 and 1, the baseline-adjusted MD lies between 10.3 and 11.2 g/L for Hb, 45.8 and 51.8 µg/L for ferritin and 9.9 and 11.2 percentage points for TSAT. Reticulocytes rose from 2.8‰ to 12.7‰ at 4 weeks and 24.1‰ at 2 months with FCM.

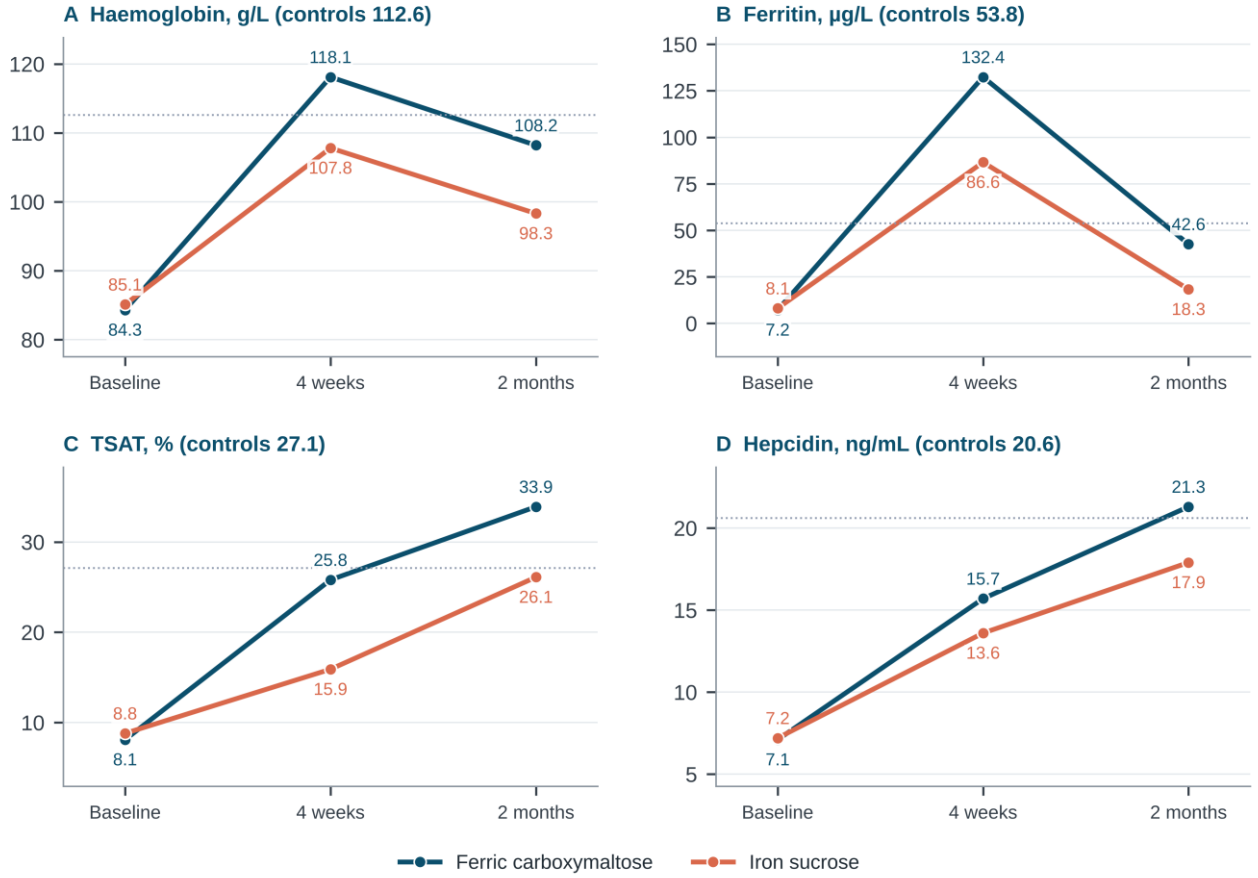
The 2-month assessment revealed a distinction that 4-week data alone conceal. As third-trimester demand and haemodilution advanced, ferritin declined in both groups, but remained above the 30 µg/L repletion threshold with FCM (42.6 ± 24.5 µg/L) while falling back into the deficient range with IS (18.3 ± 19.7 µg/L); under a log-normal distribution the geometric means were 36.9 and 12.5 µg/L (ratio 2.96, 95% CI 2.54–3.47). The regulatory axis mirrored this: hepcidin rose and EPO fell more with FCM (21.3 vs 17.9 ng/mL and 43.2 vs 47.2 mIU/mL at 2 months), consistent with completed repletion and extinction of the hypoxic erythropoietic drive, whereas EPO in the IS group remained above the control level.

Table 5. Longitudinal laboratory response and between-group effect sizes.

Marker	Ferric carboxymaltose (n = 163)			Iron sucrose (n = 167)			FCM – IS at 4 weeks		FCM – IS at 2 months
	Baseline	4 weeks	2 months	Baseline	4 weeks	2 months	MD (95% CI)	d	MD (95% CI)
Hb, g/L	84.3 ± 3.9	118.1 ± 4.2	108.2 ± 5.1	85.1 ± 3.7	107.8 ± 4.1	98.3 ± 4.8	10.3 (9.4 to 11.2)	2.48	9.9 (8.8 to 11.0)
Ferritin, µg/L	7.2 ± 2.6	132.4 ± 18.3	42.6 ± 24.5	8.1 ± 2.4	86.6 ± 14.8	18.3 ± 19.7	45.8 (42.2 to 49.4)	2.76	24.3 (19.5 to 29.1)
TSAT, %	8.1 ± 1.9	25.8 ± 3.7	33.9 ± 4.8	8.8 ± 2.1	15.9 ± 3.6	26.1 ± 4.2	9.9 (9.1 to 10.7)	2.71	7.8 (6.8 to 8.8)
Hepcidin, ng/mL	7.1 ± 2.3	15.7 ± 2.9	21.3 ± 3.5	7.2 ± 2.5	13.6 ± 2.7	17.9 ± 3.4	2.1 (1.5 to 2.7)	0.75	3.4 (2.7 to 4.1)
EPO, mIU/mL	57.3 ± 8.9	48.6 ± 7.2	43.2 ± 6.5	54.6 ± 8.3	50.4 ± 7.5	47.2 ± 7.1	–1.8 (–3.4 to –0.2)	–0.24	–4.0 (–5.5 to –2.5)
MCV, fL	82.3 ± 4.7	84.6 ± 4.3	87.9 ± 4.1	83.1 ± 5.1	84.2 ± 4.8	86.1 ± 4.5	0.4 (–0.6 to 1.4)	0.09	1.8 (0.9 to 2.7)
MCH, pg	23.5 ± 1.8	26.7 ± 1.9	28.4 ± 1.6	23.1 ± 1.6	26.2 ± 1.7	27.6 ± 1.6	0.5 (0.1 to 0.9)	0.28	0.8 (0.5 to 1.1)

Values are mean ± SD. MD, mean difference (Welch 95% CI); d, Cohen's d. Ferritin at 2 months was right-skewed (SD close to the mean); the ratio of geometric means is given in Section 3.4. EPO, erythropoietin; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; TSAT, transferrin saturation.

Figure 3. Trajectories of (A) haemoglobin, (B) ferritin, (C) transferrin saturation and (D) hepcidin after ferric carboxymaltose (teal) and iron sucrose (coral). Reference values in non-anaemic controls are shown in the panel titles.



For the four markers shown, all within-group changes from baseline and all between-group differences at 4 weeks and 2 months were significant ($p < 0.001$; Table 5). TSAT, transferrin saturation.

3.5 Target attainment, symptoms and tolerability

At 4 weeks, more women receiving FCM achieved each predefined target (Figure 4A): Hb ≥110 g/L (86.5% vs 58.7%; RR 1.47, 95% CI 1.28–1.70; NNT 4; E-value 2.31), ferritin ≥30 µg/L (97.5% vs 85.0%), normalised hepcidin (72.4% vs 51.5%) and EPO ≤45 mIU/mL (82.2% vs 58.1%). Symptom regression paralleled the laboratory response (Figure 4B): the proportion with three or more symptoms fell from 78.5% to 14.1% with FCM and from 79.0% to 28.7% with IS (RR 0.49, 0.31–0.77), and complete resolution of symptoms occurred in more than 60% of FCM recipients.

Adverse events occurred in 8.6% of FCM and 17.4% of IS recipients (RR 0.49, 0.27–0.90). Reactions were predominantly mild cutaneous (pruritus, flushing, warmth) within 20 minutes of infusion and resolved without treatment; autonomic symptoms (headache, palpitations, weakness) and combined reactions were more frequent with IS, and three women (1.8%) discontinued IS, versus none with FCM. FCM required 1.3 ± 0.5 infusions per woman versus 5.4 ± 1.1 for IS—about four fewer visits per treated woman.

Figure 4. (A) Attainment of laboratory targets at 4 weeks. (B) Prevalence of anaemia symptoms before and 4 weeks after treatment.



Light bars, baseline; dark bars, 4 weeks. EPO, erythropoietin; FCM, ferric carboxymaltose; IS, iron sucrose.

3.6 Delivery, postpartum and neonatal outcomes

Effects carried through to delivery (Table 6). Mean blood loss was 90 mL lower with FCM (380.4 ± 84.3 vs 470.1 ± 93.6 mL), and postpartum haemorrhage >500 mL was half as frequent (12.3% vs 25.7%; RR 0.48, 0.29–0.77; NNT 8). On postpartum day 3, Hb was 8.2 g/L higher, Hb <100 g/L was 72% less frequent (RR 0.28; NNT 5), repeat iron was needed less often (6.7% vs 19.2%; NNT 9) and postpartum stay was shorter (3.2 vs 3.8 days). The E-values were 3.62 (1.91 for the confidence limit) for postpartum haemorrhage >500 mL and 6.52 (3.38) for day-3 Hb <100 g/L: to explain away these effects, a confounder would have to be associated with both treatment and outcome by a risk ratio of at least 3.6 and 6.5, respectively, whereas the categorical baseline characteristics in Table 2 differed between the groups by a risk ratio of at most 1.3. Labour induction was less frequent with FCM (14.7% vs 23.4%; p = 0.046), whereas caesarean delivery and labour duration did not differ. Birthweight and fetal growth restriction were similar; transfer of the newborn to intensive or special care was less frequent after FCM (2/163 vs 10/167; Fisher p = 0.035), although the small number of events warrants caution.

Table 6. Tolerability, delivery, postpartum and neonatal outcomes: ferric carboxymaltose versus iron sucrose.

Outcome	FCM, n/N (%)	IS, n/N (%)	RR (95% CI)	ARD, % (95% CI)	NNT	p
Efficacy and tolerability						
Hb ≥110 g/L at 4 weeks	141/163 (86.5)	98/167 (58.7)	1.47 (1.28–1.70)	+27.8 (18.7 to 36.9)	4	<0.001
≥3 symptoms at 4 weeks	23/163 (14.1)	48/167 (28.7)	0.49 (0.31–0.77)	−14.6 (−23.3 to −5.9)	7	0.001
Any adverse event	14/163 (8.6)	29/167 (17.4)	0.49 (0.27–0.90)	−8.8 (−16.0 to −1.6)	12	0.018
Treatment discontinuation	0/163 (0)	3/167 (1.8)	—	−1.8	—	0.248†
Delivery and postpartum						
Caesarean delivery	46/163 (28.2)	57/167 (34.1)	0.83 (0.60–1.14)	−5.9 (−15.9 to 4.1)	—	0.247
Labour induction	24/163 (14.7)	39/167 (23.4)	0.63 (0.40–1.00)	−8.6 (−17.0 to −0.2)	12	0.046
Blood loss >500 mL	20/163 (12.3)	43/167 (25.7)	0.48 (0.29–0.77)	−13.5 (−21.8 to −5.2)	8	0.002

Outcome	FCM, n/N (%)	IS, n/N (%)	RR (95% CI)	ARD, % (95% CI)	NNT	p
Hb <100 g/L on day 3	13/163 (8.0)	47/167 (28.1)	0.28 (0.16–0.50)	–20.2 (–28.2 to –12.2)	5	<0.001
Repeat postpartum iron	11/163 (6.7)	32/167 (19.2)	0.35 (0.18–0.67)	–12.4 (–19.5 to –5.3)	9	<0.001
Neonatal						
Fetal growth restriction	11/163 (6.7)	12/167 (7.2)	0.94 (0.43–2.07)	–0.4 (–5.9 to 5.1)	—	0.876
Transfer to NICU / special care	2/163 (1.2)	10/167 (6.0)	0.20 (0.05–0.92)	–4.8 (–8.7 to –0.8)	21	0.035†
Continuous outcomes, mean ± SD						
Blood loss, mL	380.4 ± 84.3	470.1 ± 93.6	MD –89.7 (–109.0 to –70.4)			<0.001
Hb on postpartum day 3, g/L	112.4 ± 7.1	104.2 ± 8.9	MD 8.2 (6.5 to 9.9)			<0.001
Postpartum stay, days	3.2 ± 0.4	3.8 ± 1.2	MD –0.6 (–0.8 to –0.4)			<0.001
Infusions per woman	1.3 ± 0.5	5.4 ± 1.1	MD –4.1 (–4.3 to –3.9)			<0.001
Labour duration, h	8.4 ± 2.8	8.9 ± 2.9	MD –0.5 (–1.1 to 0.1)			0.11
Birthweight, g	3210 ± 270	3165 ± 285	MD 45 (–15 to 105)			0.14

Shaded rows, outcomes with the largest absolute benefit. RR, risk ratio (FCM vs IS); ARD, absolute risk difference (FCM – IS); NNT, number needed to treat to benefit; MD, mean difference (Welch 95% CI). p values from Pearson's χ^2 test or Welch's t-test; †Fisher's exact test. NICU, neonatal intensive care unit.

4 DISCUSSION

4.1 Principal findings

This study adds three linked observations to the evidence on iron deficiency in pregnancy. First, in a PHC population with a high prevalence of iron deficiency, haemoglobin-based screening missed the stages at which intervention is cheapest: half of the screened women were iron-deficient while their haemoglobin was still normal. Second, fetal haemodynamic adaptation, seen as a fall in the cerebroplacental ratio, was already measurable in prelatent deficiency, before anaemia and without a rise in umbilical artery resistance, and became a graded uteroplacental abnormality once moderate anaemia developed. Third, in moderate IDA the hepcidin–ferritin regulatory loop was intact while erythropoietin was uncoupled from haemoglobin. Single-visit, high-dose substrate replacement with FCM was associated with faster, more complete and more durable correction of this deficit than repeated iron sucrose, and with less postpartum haemorrhage, less postpartum anaemia and fewer clinic visits.

4.2 Comparison with previous studies

Our screening findings are consistent with reports that iron deficiency is common among non-anaemic pregnant women and that ferritin testing is under-used [9,10]. They also match the threshold recommended by the British Society for Haematology, which regards ferritin <30 µg/L as diagnostic of iron deficiency in pregnancy [5]. The low hepcidin concentrations in deficient women accord with longitudinal data showing that hepcidin declines in pregnancy and discriminates iron deficiency [12]. The strong hepcidin–ferritin coupling we observed, together with normal CRP, is the expected signature of absolute rather than functional iron deficiency [11].

To our knowledge, the association between prelatent iron deficiency and reduced CPR has not previously been described. Because CPR integrates fetal cerebral vasodilatation and placental resistance and predicts adverse perinatal outcome in both small and appropriately grown fetuses [15,16], a reduced CPR in the prelatent stage suggests that the fetus senses impaired oxygen delivery before the mother becomes anaemic. This is biologically plausible: iron is preferentially transferred to the fetus, but placental transfer falls when maternal stores are exhausted, and the developing brain is particularly sensitive to iron insufficiency [13,14]. The inverse correlations between maternal iron indices and uterine artery resistance in moderate IDA extend this observation to the maternal side of the placenta.

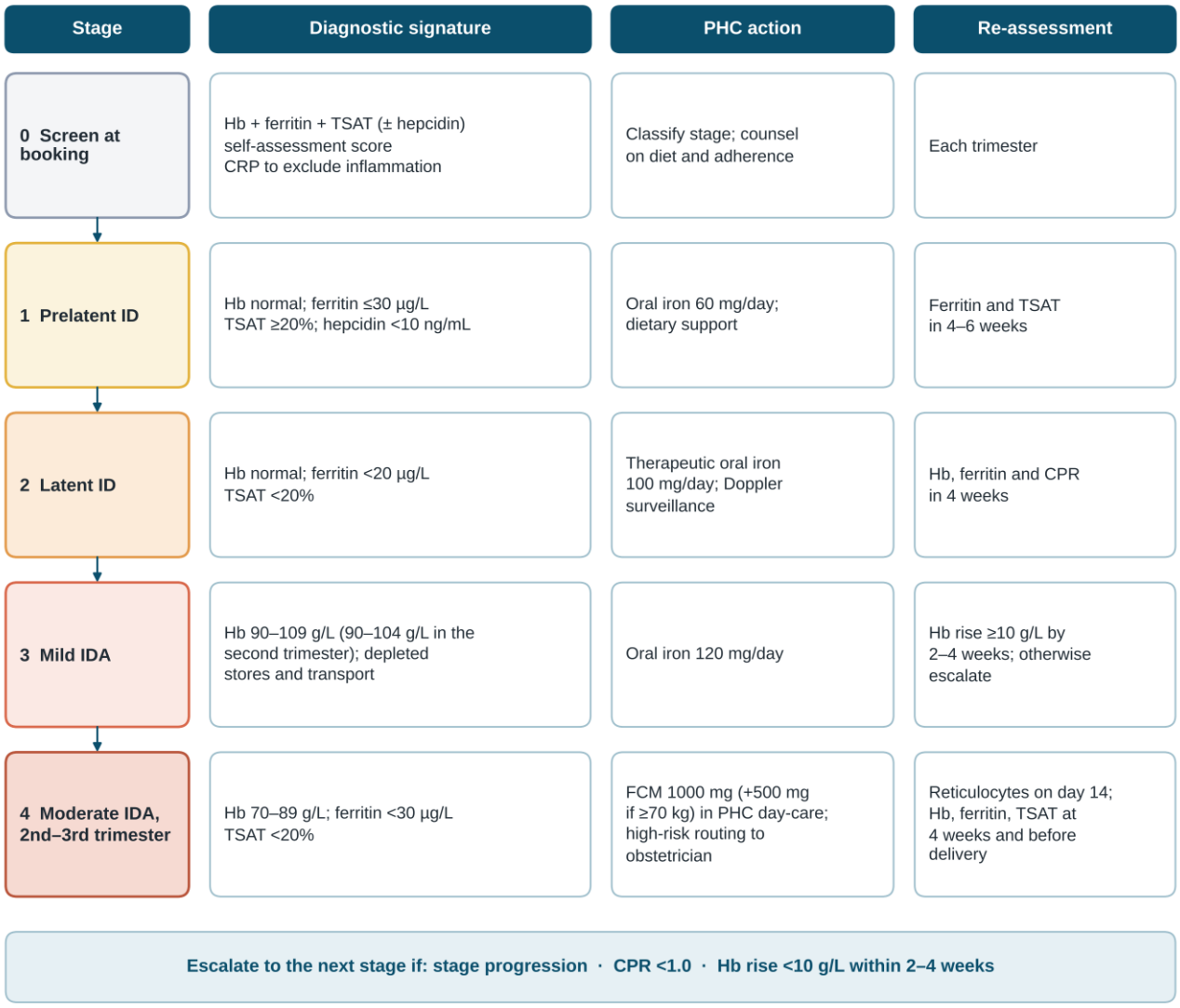
The haematological advantage of FCM over iron sucrose agrees with randomised comparisons in pregnancy [27] and with trial and meta-analytic evidence that intravenous iron raises haemoglobin faster than oral iron, with fewer adverse events [17–20]. In the FER-ASAP trial, FCM produced a faster haemoglobin rise than oral iron in pregnant women with IDA [17], and in Malawi a single second-trimester dose of FCM reduced iron deficiency and iron-deficiency anaemia at 36 weeks compared with oral iron but did not improve birthweight [18]. Recent trials have extended this evidence to low-resource primary care. In Nigeria (IVON), a single FCM dose reduced iron deficiency and IDA at 36 weeks, although overall anaemia did not differ from oral iron [21]. In REVAMP-TT, an FCM infusion given in Malawian primary health centres in the third trimester reduced anaemia before delivery [22], and in India (RAPIDIRON) single-dose intravenous iron reduced the need for additional intravenous iron or transfusion before delivery, with fewer low-birthweight infants after FCM than after oral iron [23]. Our data add a direct intravenous-versus-intravenous comparison within PHC and show that the

difference persisted at 2 months, when ferritin after iron sucrose had fallen back below 30 µg/L. The lower rates of postpartum haemorrhage >500 mL and day-3 anaemia are clinically important, because women entering labour with depleted stores have little reserve to buffer delivery blood loss, and severe peripartum anaemia is linked to maternal mortality [3]. These obstetric differences come from a non-randomised comparison and need confirmation. The lower NICU transfer rate after FCM should be regarded as hypothesis-generating, given the few events and the absence of a birthweight difference.

4.3 Implications for primary health care

The findings support a staged, multimarker approach that can be implemented within PHC (Figure 5). Ferritin and TSAT at booking would identify iron-deficient women who still have normal haemoglobin; hepcidin, where available, refines the distinction between absolute and inflammatory deficiency; and a CPR <1.0 provides an objective trigger to move from prophylactic to therapeutic dosing and to intensify surveillance. For moderate IDA, a PHC day-care pathway with one or two FCM infusions replaced on average four additional visits per woman, an advantage that is especially relevant for rural women, who made up two-thirds of the moderate-anaemia cohort and face the greatest access barriers. These principles have been incorporated into the national clinical protocol on the management of pregnant women with IDA (Ministry of Health order No. 290, 2024) [24].

Figure 5. Proposed staged diagnostic and treatment pathway for iron deficiency in pregnancy within primary health care.



Escalation is triggered by stage progression, a cerebroplacental ratio <1.0, or failure to achieve an Hb rise of ≥10 g/L within 2–4 weeks. CPR, cerebroplacental ratio; CRP, C-reactive protein; FCM, ferric carboxymaltose; ID, iron deficiency; IDA, iron-deficiency anaemia; PHC, primary health care; TSAT, transferrin saturation.

4.4 Strengths and limitations

Strengths include the real-world PHC setting across urban and rural regions with contrasting resources, the combination of store, transport, regulatory and Doppler markers in the same women, a two-month durability

assessment and clinically meaningful obstetric endpoints. Several limitations should be acknowledged. The treatment comparison was not randomised and not blinded, and adjustment was limited to sensitivity analyses of group summary data, so confounding cannot be excluded; however, baseline adjustment would widen the haematological differences, and only strong confounding (E-values 3.6 and 6.5) could account for the obstetric ones. Most baseline imbalances would bias the comparison against FCM, which started with lower haematocrit, red-cell count, ferritin and TSAT; the exception is a slightly higher reticulocyte count, which could favour an early Hb response. Doppler was performed in a single time window, which in most women of the therapeutic cohort followed the first infusion, so uteroplacental indices in moderate IDA describe the state at 24–28 weeks rather than an untreated baseline; in addition, the prelatent comparison involved a small subgroup, and CPR was interpreted with a fixed cut-off rather than gestation-specific centiles. Hepcidin assays are not standardised across platforms, and the thresholds used here require external validation. Hb at admission for delivery was not available, so the link between treatment and blood loss rests on iron stores at 2 months and on day-3 Hb. Neonatal events were few. Finally, the study was conducted in one country; generalisability to settings with different iron-deficiency epidemiology or drug costs needs confirmation in a pragmatic randomised trial with cost-effectiveness analysis.

5 CONCLUSIONS

Iron deficiency in pregnancy is a staged continuum in which fetal haemodynamic adaptation begins before anaemia. In PHC, haemoglobin-only screening should give way to multimarker staging with ferritin and TSAT, supported by hepcidin and Doppler where available. For moderate iron-deficiency anaemia in the second and third trimesters, single-visit ferric carboxymaltose delivered in PHC day-care was associated with faster, more complete and more durable repletion than iron sucrose, with fewer adverse events, less postpartum haemorrhage and anaemia, and far fewer clinic visits. A randomised trial is needed to confirm these findings.

DECLARATIONS

Ethics approval and consent. Local ethics committee of the Tashkent Medical Academy, now Tashkent State Medical University (protocol No. 11-07/16612, 5 November 2021); written informed consent from all participants.

Trial registration. Not applicable: observational cohort study of routine care, not registered in a clinical-trial registry (Section 2.1).

Author contributions (CRediT). GTD: conceptualisation, investigation, formal analysis, writing – original draft; DKN and BMM: supervision, methodology, writing – review and editing; IK, MS and US: investigation, data curation. All authors approved the final manuscript.

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Data availability. De-identified data are available from the corresponding author on reasonable request.

Use of AI-assisted tools. Claude (Anthropic) was used to assist with drafting, language editing and formatting of the manuscript. The authors reviewed and edited the text and take full responsibility for the content.

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