Treatment of Iron Deficiency: A New Paradigm

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Relevant Disclosures

- Funding for data management (only) from Covis Pharma
- Educational, non-promotional programs for Pharmacosmos

Learning Objectives

1. Distinguish the need for oral or intravenous iron for the treatment of iron deficiency
2. Familiarize and become comfortable with the available IV iron formulations
3. Be able to differentiate the symptoms associated with minor infusion reactions with IV iron and the rare symptoms of severe hypersensitivity which can lead to anaphylaxis
4. Review evidence based treatment approaches with iron supplementation in specific conditions associated with iron lack

History of Oral Iron

- Sydenham first used iron filings in cold wine in 1500s to treat “green sickness” (described by Lange) in 1687
- Blaud renamed “chlorosis” in 1832, First to use ferrous sulfate
- By time of American Civil War iron was used to treat war wounds
- Today iron deficiency is the most common micronutrient deficiency on the planet estimated to affect >35% of world’s population, >50% of gravidas
- 100 times more prevalent than cancer
- >500 years later, the often ineffective, usually poorly tolerated oral iron continues to be frontline

Beard JL, et al. Annu Rev Nutr. 2001:23:41-58

Iron Deficiency in Non-pregnant Women

- Almost three billion cases worldwide
- In top five causes of years lived with disability worldwide
- Leading cause of years lived with disability in LMIC countries
- Leading cause of years lived with disability across 35 countries

- Pasricha et al, Lancet, 2021

JAMA Network Open

Original Investigation | Nutrition, Obesity, and Exercise

Evaluation of Hemoglobin Cutoff Levels to Define Anemia Among Healthy Individuals

O. Yaw Addo, PhD; Emma X. Yu, MPH; Anne M. Williams, PhD; Melissa Fox Young, PhD; Andrea J. Sharma, PhD; Zuguo Mei, MD; Nicholas J. Kassebaum Maria Elena D. Jefferds, PhD; Parminder S. Suchdev, MD

JAMA Network Open. 2021;4(8):e2119123. doi:10.1001/jamanetworkopen.2021.19123

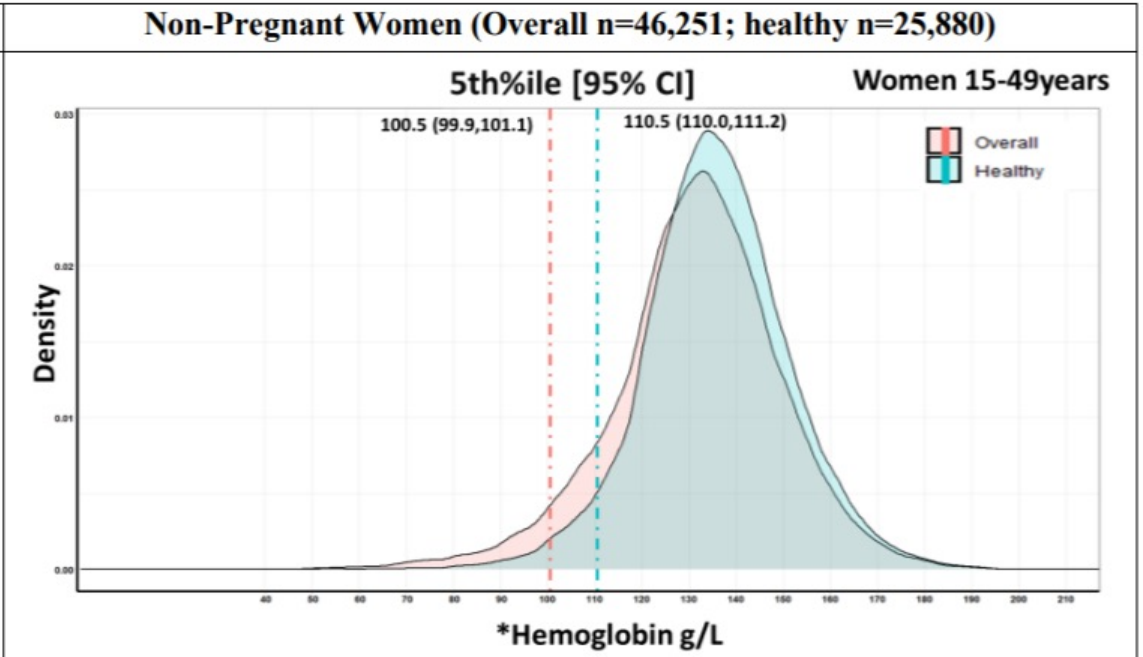


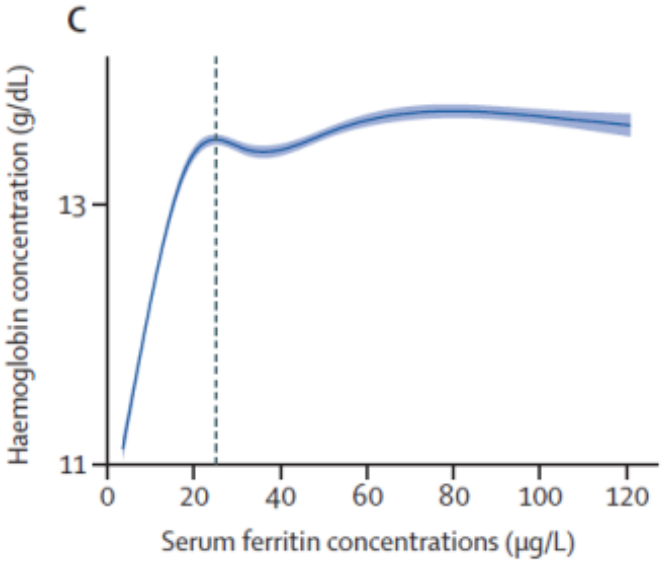
Table 1. Descriptive Characteristics and Prevalence of Selected Biological Indicators Among the Total Sample and Apparently Healthy Subsample in a Multinational Sample

Characteristic	Participants, No. (%)			
	Preschool children aged 6-59 mo		Nonpregnant women aged 15-49 y	
	Overall (n = 33 699)	Healthy subgroup (n = 13 445)	Overall (n = 46 251)	Healthy subgroup (n = 25 880)
Age, mean (SD), mo for children or y for women	29.9 (15.6)	32.9 (16.0)	31.0 (9.5)	30.9 (9.9)
Sex				
Male	17 391 (51.6)	6750 (50.2)	0	0
Female	16 308 (48.4)	6695 (49.8)	46 251 (100.0)	25 880 (100.0)
Biomarkers and infection, % (95% CI)				
Iron deficiency	22.1 (21.6-22.5)	NA	21.2 (20.8-21.6)	NA
Vitamin A deficiency				NA
Inflammation	32.7 (32.2-33.3)	NA	21.9 (21.5-22.3)	NA
Malaria	26.0 (24.9-27.0)	NA	12.7 (11.8-13.7)	NA
Anemia	40.9 (40.4-41.4)	23.4 (22.6-24.1)	22.3 (21.9-22.7)	13.0 (12.6-13.4)
Blood draw method				
Venous	14 628 (46.4)	5104 (38.0)	23 759 (52.4)	13 904 (53.7)
Capillary	16 885 (53.6)	8341 (62.0)	21 586 (47.6)	11 976 (46.3)
Hb assessment method				
Automated hematology analyzer	3150 (10.0)	2276 (16.9)	11 733 (25.9)	7883 (30.5)
Hemocue model				
Hb-B	3148 (10.0)	939 (7.0)	863 (1.9)	568 (2.2)
201+	22 925 (72.7)	9277 (69.0)	29 193 (64.4)	14 946 (57.8)
301	2290 (7.3)	956 (7.1)	3556 (7.8)	2486 (9.6)

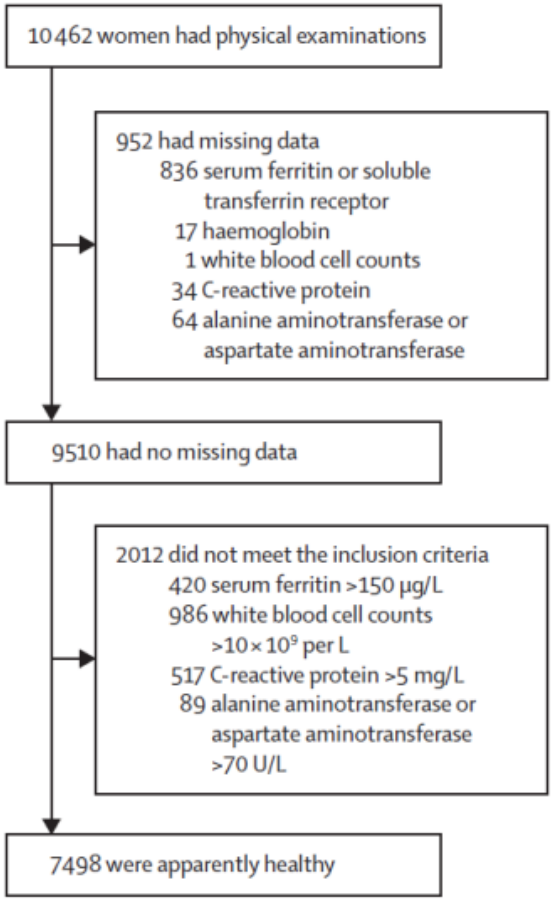
Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional study

Zuguo Mei, O Yaw Addo, Maria Elena Jefferds, Andrea J Sharma, Rafael C Flores-Ayala, Gary M Brittenham

www.thelancet.com/haematology Vol 8 August 2021



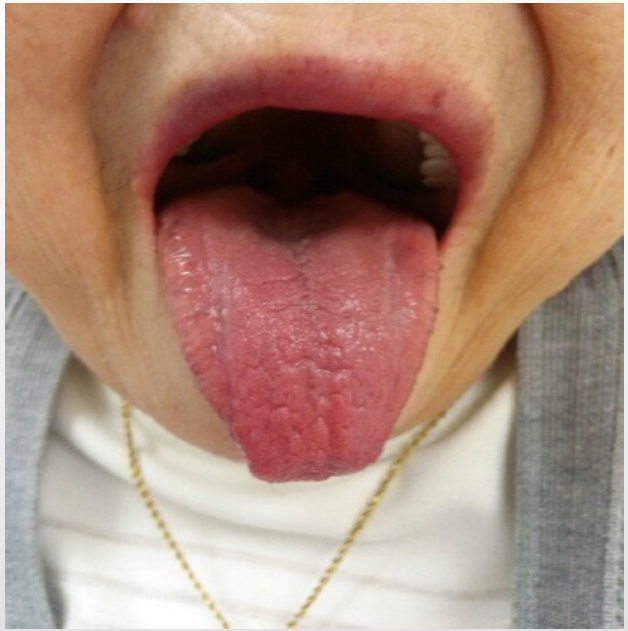
Ferritin 25.2 (24.2-26.2)



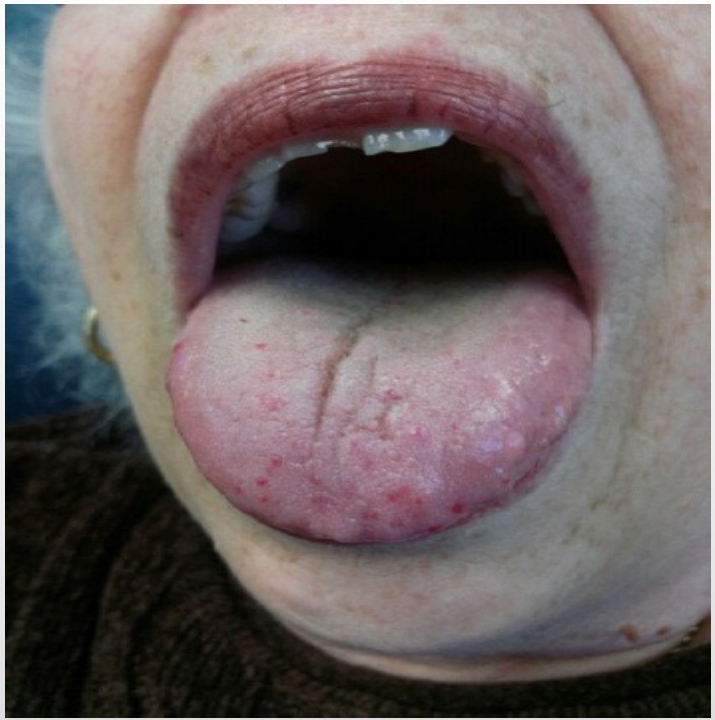
Symptoms of Iron Deficiency

- Fatigue often independent of hemoglobin
- Pagophagia and forms of pica
- Restless Legs Syndrome
- Brittle Integument

Pretreatment Tongue



Healed Tongue

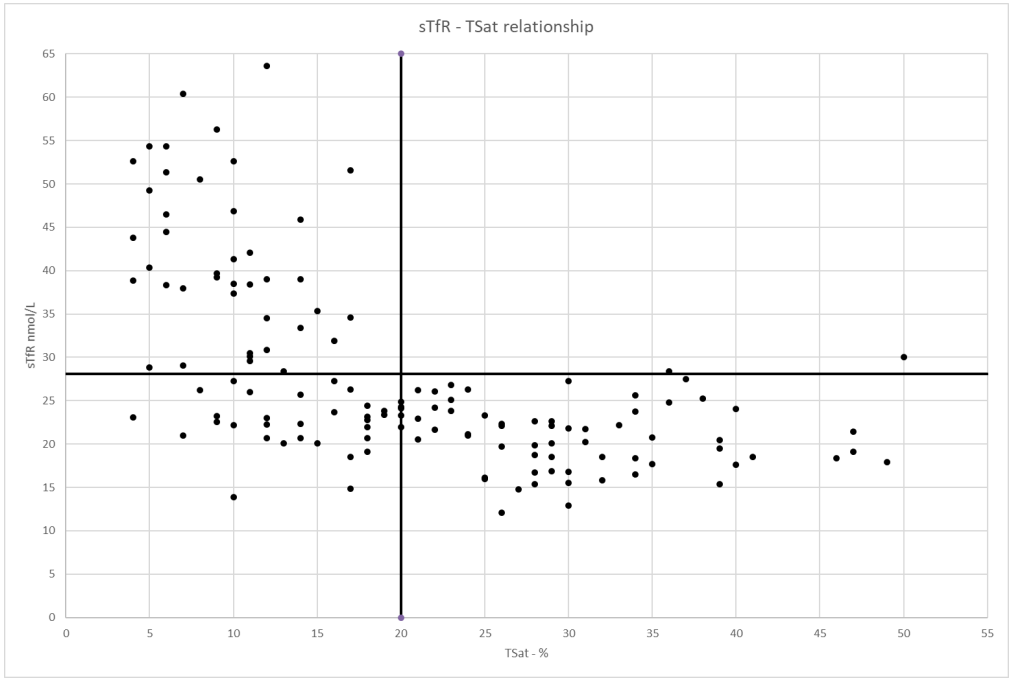


Diagnosis

	Iron Deficiency Anemia	Anemia of Inflammation
	Iron deficiency	**Anemia of Inflammation**
CHr	Low	Low
* **TIBC**	High	Low
Transferrin saturation	Low	Low
* **Serum ferritin**	Very low	N/High

Nairz M, et al. *Wien Med Wochenschr*. 2016.

Correlation of TSAT and soluble transferrin receptor (sTfR) in iron deficiency



This graph was generated using data from 52 healthy young non-anemic adults, none of whom was receiving iron supplementation, with two or three blood samples taken from each individual over the course of several weeks.
Figure courtesy of Dr Matthew Frise using data from [27140401 and 35046429]

Oral or Intravenous Iron

Indications for oral iron

- Mild, uncomplicated iron deficiency without active bleeding
- First trimester of pregnancy
- Second trimester of pregnancy if Hb>10.0 g/dL

Indications for IV iron

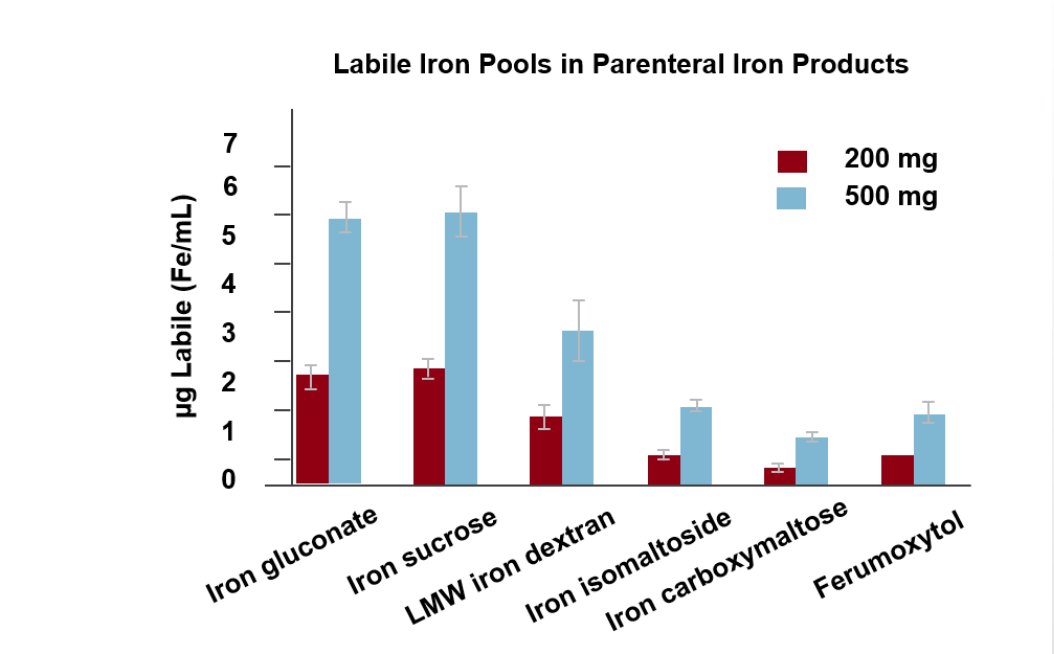
- Intolerance of, or unresponsiveness to oral iron
- Second trimester of pregnancy if Hb<10.0 g/dl
- Third trimester of pregnancy
- After bariatric surgery
- Abnormal uterine bleeding
- Inflammatory bowel disease
- Angiodysplasia (HHT)
- Iron restricted erythropoiesis
- Co-morbid “inflammatory” condition

Intravenous Iron Preparations

Carbohydrate	Total Dose Infusion (TDI)	Test Dose Required	Boxed warning	Availability
LMW Iron dextran	YES	Yes	Yes	US/Eur
Ferric gluconate	No	No	No	US/Eur
Iron sucrose	No	No	No	US/Eur
Ferumoxytol	YES	No	Yes	US
Carboxymaltose	YES	No	N/A	US/Eur
Derisomaltose	YES	No	N/A	NA/Eur

1. INFeD. Available at: http://pi.actavis.com/data_stream.asp?product_group=1251&p=pi&language=E.
2 . Ferrlecit. Available at: http://www.products.sanofi-aventis.us/ferrlecit/ferrlecit.pdf.
3 . Venofer. Available at: http://www.venofer.com/PDF/Venofer_IN2340_Rev_9_2012.pdf.
4. Feraheme. Available at: http://www.feraheme.com/downloads/feraheme-pi.pdf.
5 . Injectafer. Available at: http://www.injectafer.com/files/Prescribing_Information.pdf.
6 . Monofer. Available at: http://www.nataonline.com/sites/default/files/imagesC/Monofer_core_SPC.pdf.

Labile Iron Content in Parenteral Iron Products



Used with permission from: Jahn MR, Andreasen HB, Fütterer S, Nawroth T, Schünemann V, Kolb U, Hofmeister W, Muñoz M, Bock K, Meldal M, Langguth P. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. Eur J Pharm Biopharm. 2011 Aug;78(3):480-91.

Intravenous iron formulations permitting total dose infusion

Trade Name	INFeD-US Cosmofer-Europe	Feraheme*	Injectafer-US Ferinject-Europe	Monoferric- US Monofer-Europe
Manufacturer	AbbVie	Covis	Daiichi Sankyo	Pharmacosmos
Carbohydrate	Low molecular weight iron dextran	Ferumoxytol	Carboxymaltose	Derisomaltose
Total dose infusion (TDI) **Test dose required**	Yes Yes	No No	Yes- Europe/ No- US No	Yes No
Approved dose	100 mg per dose- US 20 mg/kg- EU	510 mg	750 mg- US 1000 mg- Europe	1000 mg if ≥50 kg- US 20 mg/kg- EU
Optimal dose **Infusion time**	1000 mg 60 minutes	1020 mg 30 minutes	1000 mg EU 750 mg x 2 US 15 minutes	1000 mg 20 minutes

*Only available in the US

Adverse Events with Iron Supplementation

ORAL (70%)

- Constipation (less often diarrhea)
- Metallic taste
- Nausea
- Gastric Cramping
- Thick, green, tenacious stool

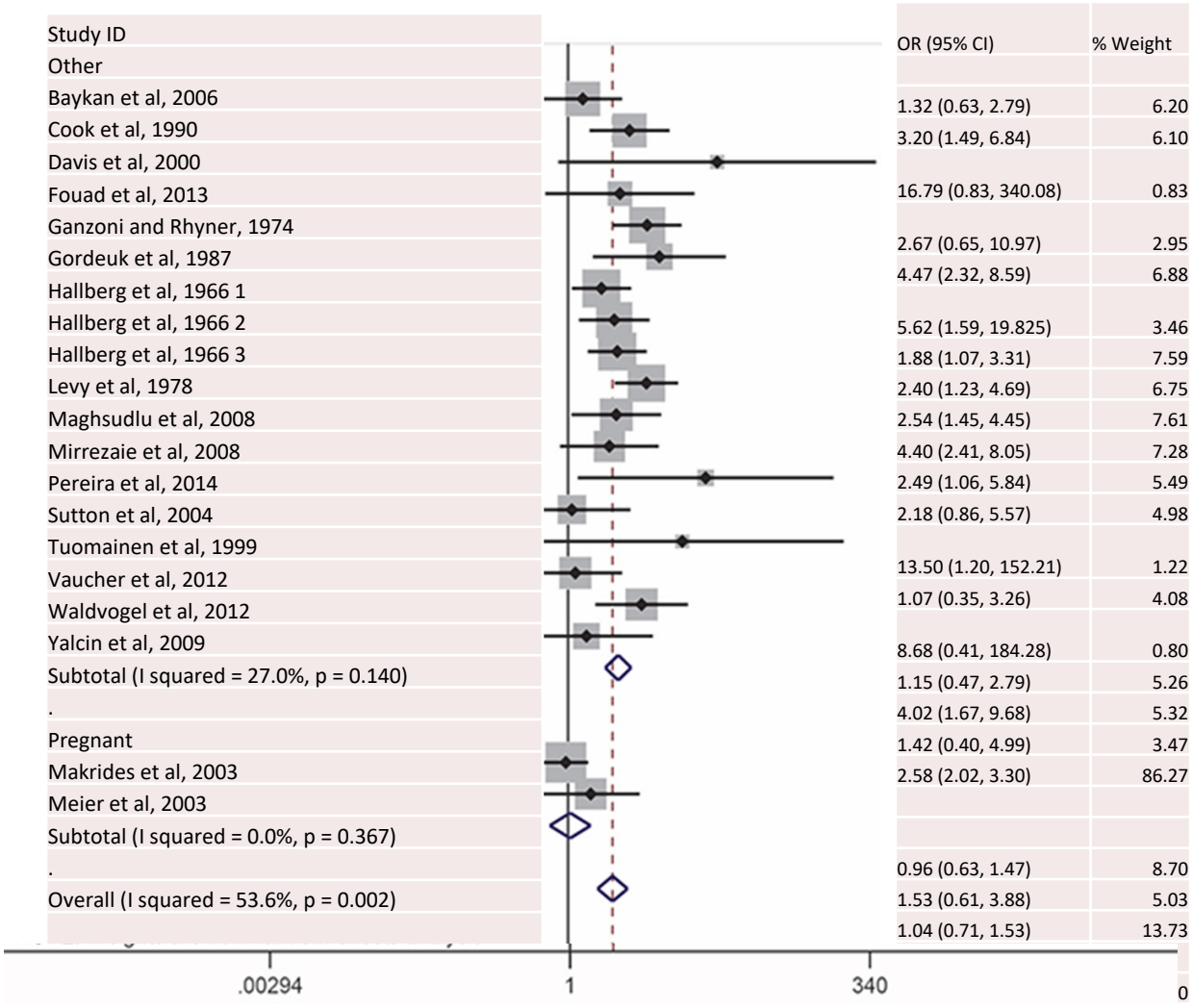
INTRAVENOUS

Infusion Reactions (1-3%)

- Pressure in chest
- Arthralgia or myalgia
- Headache
- Flushing

Severe Hypersensitivity (<1:250,000)

- Hypotension
- Wheezing
- Stridor
- Periorbital edema



Forest plot for the effect of daily ferrous sulfate supplementation on the incidence of gastrointestinal side-effects in placebo-controlled RCTs.

With Permission: Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015 Feb 20;10(2):e0117383

Once vs Twice Daily Dosing

	Once Daily Dosing (120 mg single dose)				Twice Daily Dosing (60 mg BID)			
	Day 1	Day 2	Day 3	Days 1-3	Day 1	Day 2	Day 3	Days 1-3
Fractional iron absorption, %	16.8 (11.0, 25.7)	10.1 (6.7, 15.1) §	9.7 (6.0, 15.6) §	11.8 (7.1, 19.4)	19.1 (13.7, 26.7)	11.0 (7.3, 16.4) §	10.6 (7.1,15.9) §	13.1 (8.2, 20.7)
Total iron absorbed, mg	17.5 (8.2, 37.3)	10.8 (5.6, 20.7) §	10.4 (5.2, 20.7) §	44.3 (29.4, 66.7)	19.8 (9.5, 41.3)	11.7 (6.0, 22.7) §	11.4 (5.9, 21.9) §	49.4 (35.2,69.4)
Serum hepcidin, nM	0.75 (0.40, 1.41)	2·77 (0·88, 8·69) §	1.79 (0.77, 4.18) §¶	1.53 (0.54, 4.32) #	0.91 (0.40, 2.08)	4.69 (2.01, 10.98) §	2.77 (1.53, 5.02) §	2.24 (0.80, 6.25)

§ Compared to Day 1 ($P<0.001$) ¶ Compared to Day 2 ($P<0.05$) # Compared to twice daily dosing ($P<0.05$)

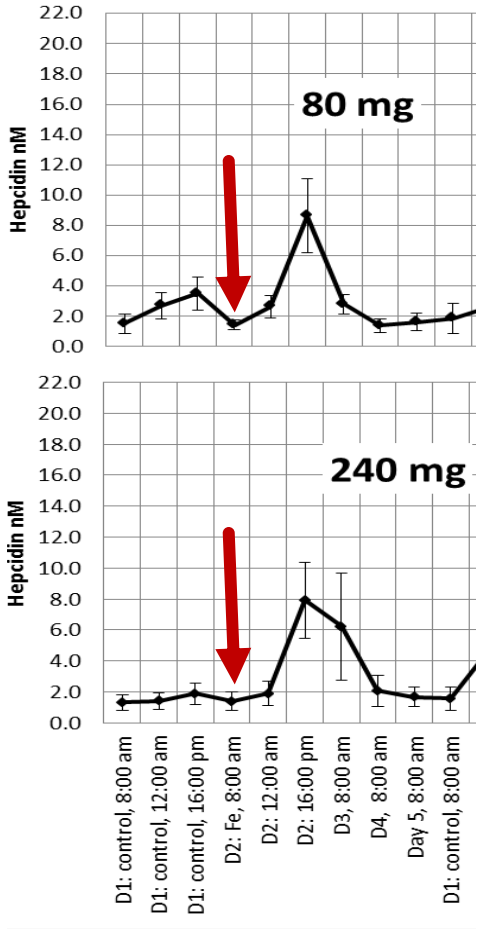
Stoffel NU, Cercamondi CI, Brittenham G, et al. The Lancet Haematology 2017, in press.

Cumulative fractional and total iron absorption in study 1

	Consecutive-day dosing for 14 days	Alternate-day dosing for 28 days	p value
Fractional iron absorption, %			
Week 1, first seven doses	16·1 (8·9, 28·9)	21·3 (13·2, 34·3)	0·13
Week 2, second seven doses	16·6 (9·4, 29·6)	22·3 (13·9, 35·8)	0·11
All 14 doses	16·3 (9·3, 28·8)	21·8 (13·7, 34·6)	0·0013
Total iron absorption, mg			
Weeks 1 and 2, first seven doses	66·9 (36·9, 121·1)	88·0 (54·8, 141·4)	0·13
Weeks 3 and 4, second seven doses	69·3 (39·3, 122·2)	92·7 (58·8, 146·2)	0·11
All 14 doses	131·0 (71·4, 240·5)	175·3 (110·3, 278·5)	0·0010

Data are geometric means (–SD, +SD). Analysed with mixed-effect models with group as fixed factor and participant as random factor (fixed-effect estimation obtained with bootstrapping).

Stoffel N, Cercamondi C, Brittenham G, Zeder C, Geurts-Moespot A, Swinkels D, Moretti D, Zimmermann, M. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *The Lancet Haematology* 2017; 4: 524–33. doi:10.1016/s2352-3026(17)30182-5.



Change in plasma hepcidin after a single oral dose of iron

Hepcidin increases >5 fold after a single dose

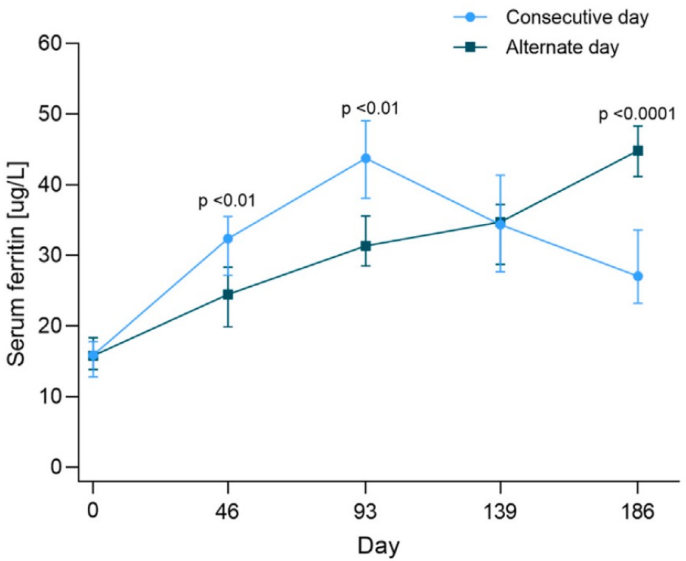
Peaks at 8h,

Elevated at 24h, but not 48h

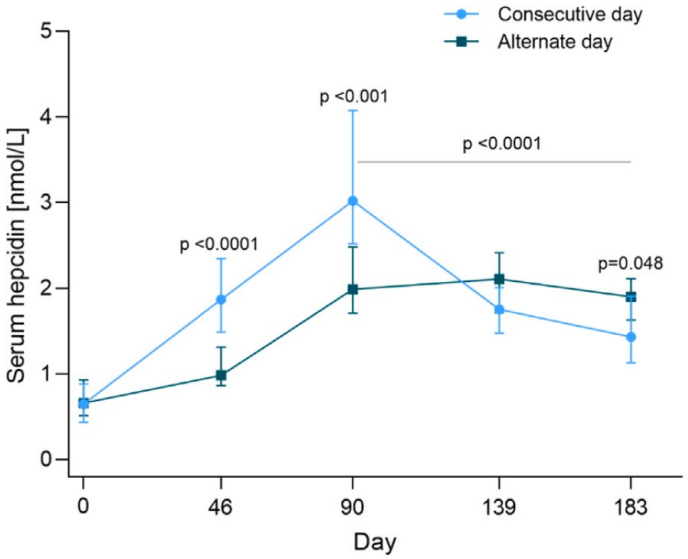
Moretti et al. Blood 2015

No difference in ferritin at the end of the study period in each group

No difference in ferritin at the end of the study period

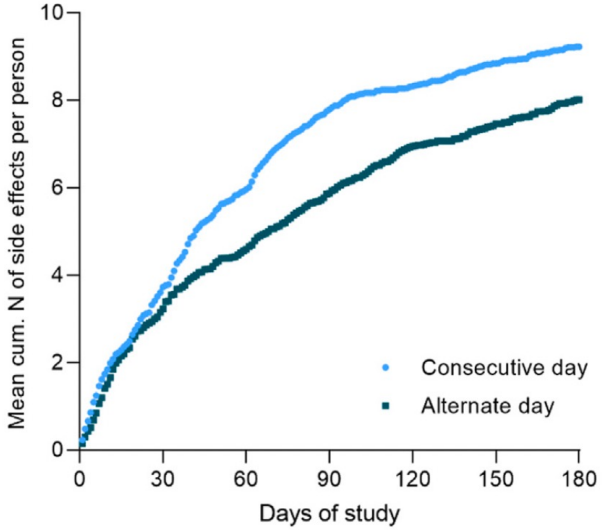


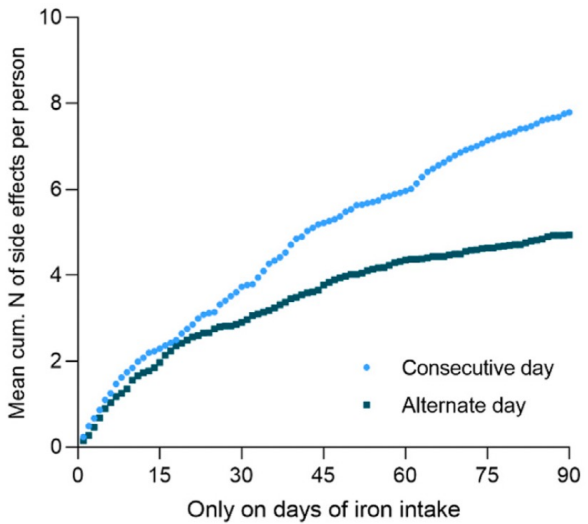
Median hepcidin was 3.0 nM vs 1.9 nM (P < 0.0001)



von Siebenthal et al. EClinicalMedicine. 2023

Alternate day oral iron reduces iron deficiency with fewer GI side effects compared with consecutive day dosing





LPR 1.56 (95% CI: 1.38, 1.77; P < 0.0001)

von Siebenthal et al. EClinicalMedicine. 2023

IV Iron Safety

- A total of 103 trials performed between 1965 and 2013 were included
- Pooled together, 10,391 patients were treated with IV iron and were compared to:
  - 4,044 patients treated with oral iron
  - 1,329 with no iron
  - 3,335 with placebo
  - 155 with IM iron

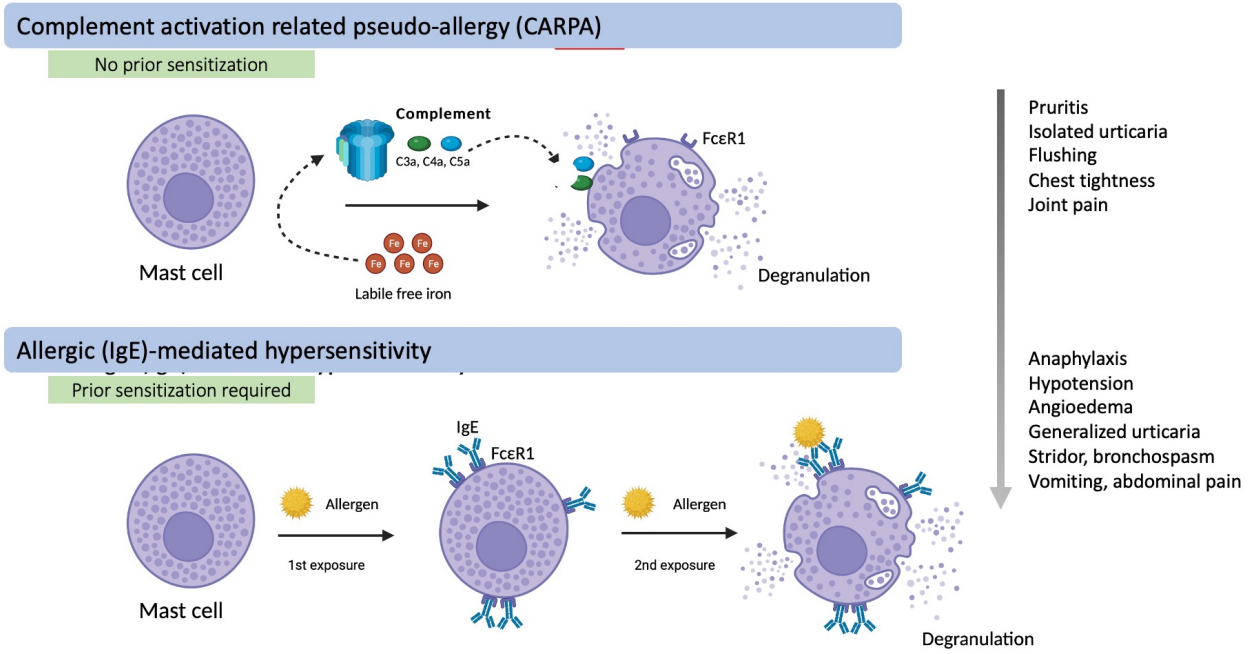
Avni et al, *Mayo Clin* 2015;90:12-23

IV Iron Safety

- Overall, there was no increase in the risk of severe adverse events (SAEs) with IV iron compared to control, RR 1.04 (95% CI 0.93-1.17, 97 trials, I^2=9%)
- No difference in either efficacy or toxicity among the formulations was observed

Avni et al, *Mayo Clin* 2015;90:12-23

Infusion reactions (IgE-mediated vs. CARPA)



Adapted from Alsaleh et al. Front Immunol. 2020

FIRM study
Powered to assess risk of HSRs

- Randomised, multi-center, double-blind trial ferumoxytol compared to ferric carboxymaltose (FCM) for treatment of IDA
- Study performed at the request of the US FDA
- Designed to formally investigate rates of HSRs

FCM=ferric carboxymaltose; FDA=Food and Drug Administration;
FER=ferumoxytol; HSR=hypersensitivity reaction; IDA=iron deficiency anaemia

Adkinson et al. Am J Hematol. 2018

Methods - endpoints

Primary endpoint:

- Incidence of moderate-to-severe HSRs, including anaphylaxis, or moderate-to-severe hypotension

Secondary safety endpoint:

- Incidence of moderate-to-severe HSRs, including anaphylaxis, serious cardiovascular events, and death

- An independent Clinical Events Committee (CEC) assessed and adjudicated all potential HSRs, moderate-to-severe hypotension, and deaths

Adkinson et al. Am J Hematol. 2018

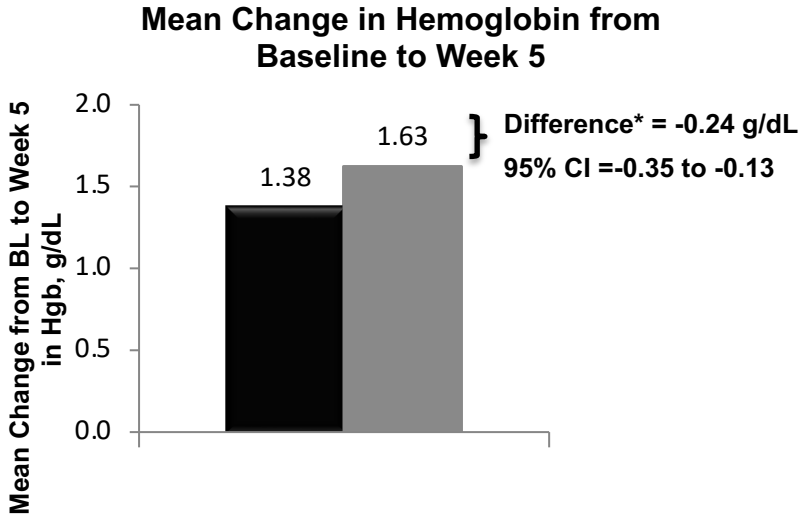
Primary endpoint composites and components

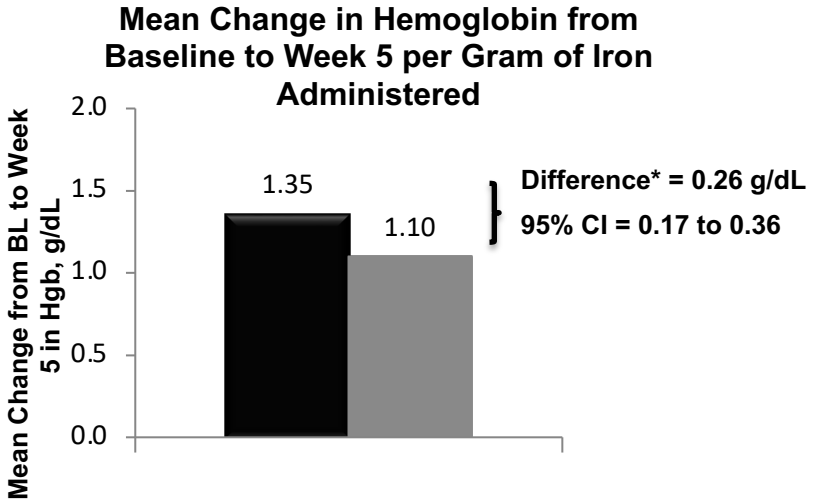
	Treatment group, n (%)		Treatment difference (95% CI)	Relative risk (95% CI)	Non-inferiority p-value
	FERUMOXYTOL (n=997)	FCM (n=1000)			
Primary endpoint – composite incidence of:	6 (0.6)	7 (0.7)	-0.1 (-0.8 to 0.6)	0.9 (0.3–2.5)	0.0001[a]
Moderate hypersensitivity reaction	3 (0.3)	6 (0.6)			
Severe hypersensitivity reaction	1 (0.1)	0 (0.0)			
Anaphylaxis	0 (0.0)	0 (0.0)			
Moderate hypotension	2 (0.2)	1 (0.1)			
Severe hypotension	0 (0.0)	0 (0.0)			

a) From non-inferiority test using a large sample assumption (Wald) with margin of 2.64% at α=0.025 level for the rate difference; exact 95% CI for treatment difference, -0.91% to +0.70%
CI=confidence interval; FCM=ferric carboxymaltose

Adkinson et al. Am J Hematol. 2018

Change in hemoglobin from baseline to week 5





- **Ferumoxytol 1020 mg (n = 997)** **Baseline Hb: 10.42**
- **Ferric Carboxymaltose 1500 mg (n = 1000)** **Baseline Hb: 10.39**

***adjusted for differences in baseline Hb**

Ferumoxytol was shown to be non-inferior to Ferric Carboxymaltose
(Lower bound of the 95% CI > -0.5 g/dL)

Adkinson et al. Am J Hematol. 2018
Slide provided as a courtesy of AMAG Pharmaceuticals, Inc

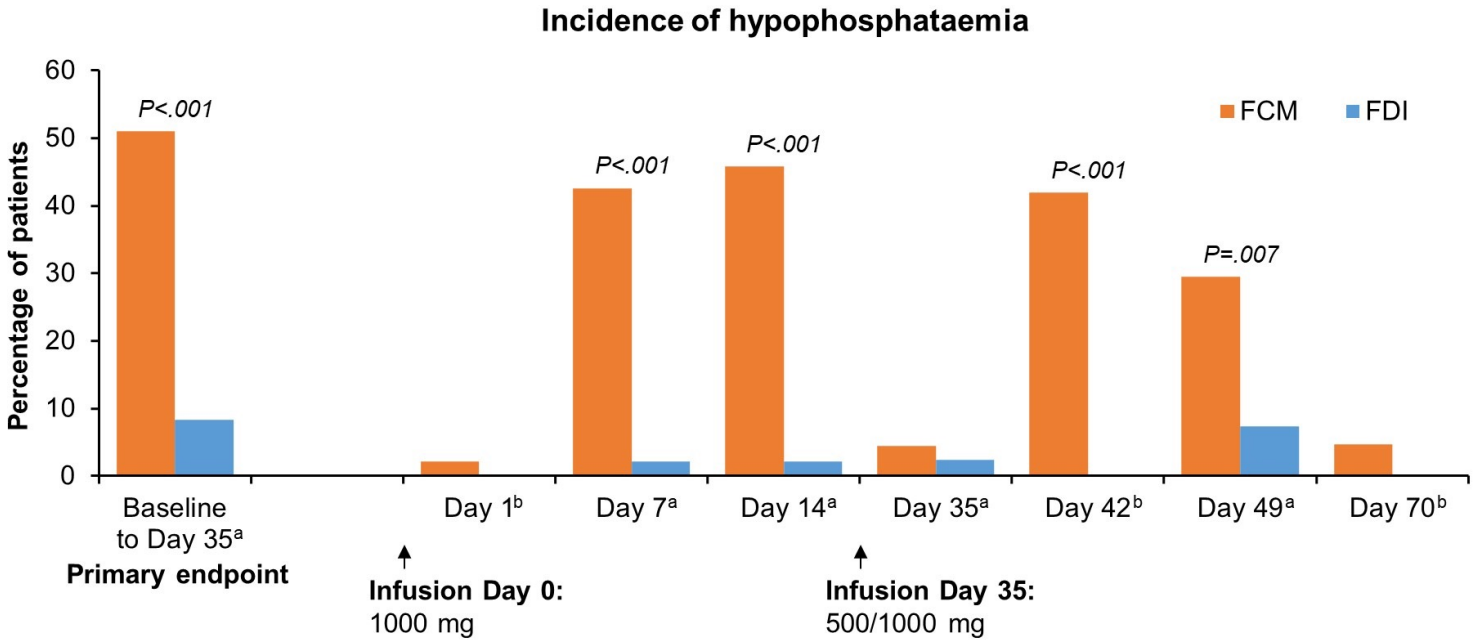
PHOSPHARE-IDA04/IDA05 trials

Hypophosphatemia

Adverse Drug Reactions[a]	No. (%)					
	Trial A		Trial B		Pooled	
	Iron Isomaltoside (n = 63)	Ferric Carboxymaltose (n = 60)	Iron Isomaltoside (n = 62)	Ferric Carboxymaltose (n = 57)	Iron Isomaltoside (n = 125)	Ferric Carboxymaltose (n = 117)
Any adverse drug reaction	7 (11.1)	27 (45.0)	14 (22.6)	28 (49.1)	21 (16.8)	55 (47.0)
Specific adverse drug reactions						
Hypophosphatemia	0	12 (20.0)	2 (3.2)	14 (24.6)	2 (1.6)	26 (22.2)
Blood						
Phosphorus decreased	0	12 (20.0)	0	7 (12.3)	0	19 (16.2)
Parathyroid hormone increased	0	1 (1.7)	4 (6.5)	5 (8.8)	4 (3.2)	6 (5.1)
Headache	1 (1.6)	1 (1.7)	3 (4.8)	4 (7.0)	4 (3.2)	5 (4.3)
Nausea	0	4 (6.7)	1 (1.6)	4 (7.0)	1 (0.8)	8 (6.8)
Serum ferritin increased	0	0	0	3 (5.3)	0	3 (2.6)

Wolf et al. JAMA. 2020

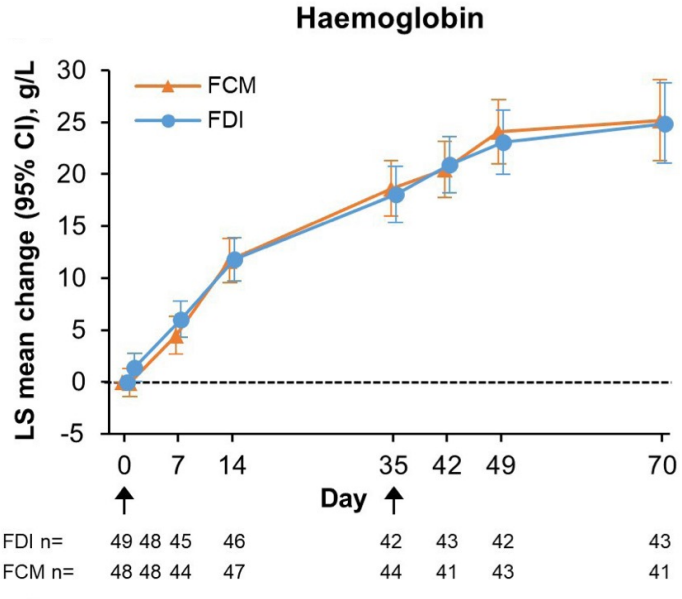
Phosphare-IBD
Hypophosphatemia

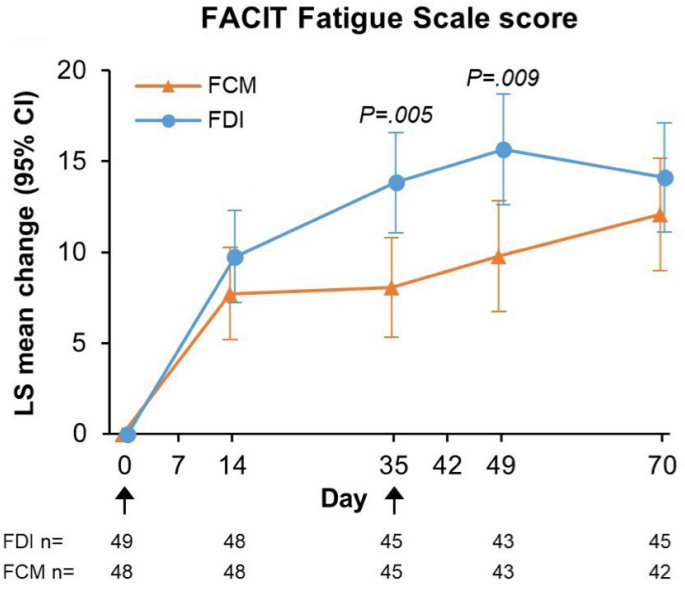


FCM=ferric carboxymaltose; FDI=ferric derisomaltose

Zoller H et al. Gut. 2022

Changes in hemoglobin and FACIT fatigue score

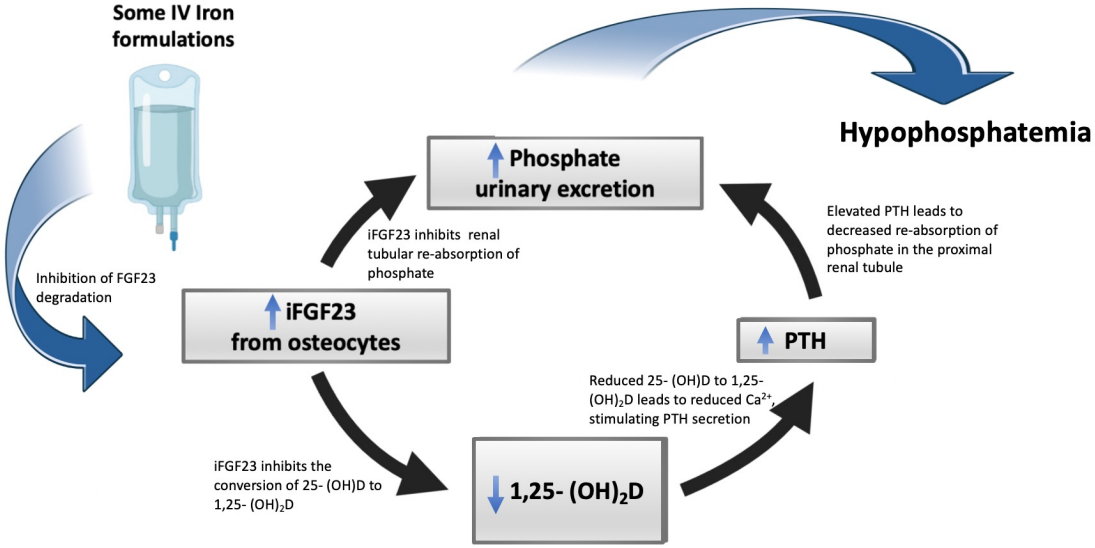




FCM=ferric carboxymaltose; FDI=ferric derisomaltose;
FACIT = Functional Assessment of Chronic Illness Therapy

Zoller H et al. Gut. 2022

Mechanism of treatment-emergent hypophosphatemia



Adapted from Blumenstein et al. Expert Opin Drug Saf. 2021

A closer look

Making the case against inferential surrogate studies

Comparative Risk of SAEs/Anaphylactic Reactions Associated with IV Iron Products

- **Wang et al. *JAMA*, 2015**
  - Retrospective new user cohort study of IV iron recipients
  - N=688,183
  - Enrolled in **U.S. Medicare** 1/2003–12/2013
  - SAEs were extremely rare in an older and sicker population
  - Anaphylaxis more likely with iron dextran vs all non-dextran IV iron products combined (iron sucrose, ferric gluconate, ferumoxytol) (P<0.001)

Wang C et al. JAMA. 2015

Comparative Risk of SAEs/Anaphylactic Reactions Associated with IV Iron Products

Risk of Anaphylaxis at First Administration by IV Iron Products

	2003–2013		2003–2013			2010–2013			
IV Iron	Non-dextran	Iron Dextran	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
No. of anaphylaxis cases	107	167	45	167	34	21	28	66	16
No. of new users	440,683	247,500	264,166	247,500	94,400	134,836	82,117	77,935	34,029
Rate per 100,000 persons (95% CI)	24.3 (20.0–29.5)	67.5 (57.8–78.7)	17.0 (12.6–23.0)	67.5 (57.8–78.7)	36.0 (25.3–50.9)	15.6 (9.9–24.3)	34.1 (23.1–50.0)	84.7 (66.0–108.4)	47.0 (27.8–78.2)
AOR (95% CI)	1 [reference]	2.6 (2.0–3.3)	1 [reference]	3.6 (2.4–5.4)	2.0 (1.2–3.5)	1 [reference]	2.2 (1.1–4.3)	5.4 (3.0–9.8)	3.0 (1.4–6.5)
P value		<0.001		<0.001	0.005		0.02	<0.001	0.001

Wang C et al. JAMA. 2015

Iron dextran had a significantly lower risk of a fatal reaction on the day of iron administration

	Non-dextran iron	Iron dextran	Iron sucrose	Iron gluconate	Ferumoxytol
"Anaphylaxis" on day of administration	107	167	45	34	28
Fatality on day of administration	36	10	19	11	6
No. of patients	440 683	247 500	264 166	94 400	82 117
Rate of "anaphylaxis" per 100 000 patients	24.3	67.5	17.0	36.0	34.1
Rate of fatality per 100 000 patients	**8.2**	**4.0**	7.2	11.7	7.3

This data shows that:

It is twice as likely to have a fatality with a non-dextran iron than with iron dextran*

* p-value = 0.04 as calculated by Poison-based test

Adapted from Wang C et al. JAMA. 2015

Comparative Risk of SAEs/Anaphylactic Reactions Associated with IV Iron Products

- **Dave et al. *Ann Intern Med*, 2022**
  - Used **Medicare coding as surrogates** for anaphylaxis and, subsequently, impossible to tell if real or iatrogenic
  - **Missed over 90% of doses administered over study period**
  - Methodological flaws, including evaluating one agent while being administered by a now proscribed method, markedly misrepresented real-world safety profiles
  - **37 world renowned key thought leaders wrote to *Ann Intern Med* editor to retract study due to "seriously flawed" methodologies**

Dave C, et al. Ann Intern Med. 2022

Comparative Risk of SAEs/Anaphylactic Reactions Associated with IV Iron Products

- **Samuelson Bannow B**, *Ann Intern Med* (ACP Journal Club), 2022 (in response to Dave C et al. *Ann Intern Med,* 2022)

  – Even in the population at higher risk for anaphylaxis (based on age), Dave and colleagues confirmed that *anaphylaxis rates with IV iron are low (<1 in 1,000) across formulations*

  – Despite 8-fold increased risk found in study, the absolute risk difference was small: **0.086%**

Comparative Risk of SAEs/Anaphylactic Reactions Associated with IV Iron Products

- **Samuelson Bannow B**, *Ann Intern Med* (ACP Journal Club), 2022 (in response to Dave C et al. *Ann Intern Med,* 2022)

- **Real-world applications in the clinic**
  - Number of infusions and associated costs often form basis of clinical decisions
  - Clinical nature of iron deficiency must be considered when making IV iron formulation selection
    - **Chronic daily blood loss may result in iron losses >1,000 mg monthly**
    - **Pregnancy and perioperative scenarios may necessitate urgent and rapid repletion**
    - **In patient-centric settings requiring IV iron, it is unclear whether an absolute risk differential of 0.086% is clinically relevant or actionable**

Inferential surrogates reinforce harmful stigmas

- Thousands of patients have been studied prospectively head-to-head showing minimal difference in relative safety among IV iron formulations

- *Suggesting that IV iron safety concerns warrant surrogate studies leads to obfuscation of the objective trial data, thus misrepresenting relative IV iron safety, propagating stigma, and harming patient care*

- Head-to-head studies are the only credible way to make conclusions about relative safety of IV iron products, but given the overwhelming preponderance of objective data supporting the safety of IV iron as a pharmacologic class, these studies are not warranted

Comparative Risk of SAEs/Anaphylactic Reactions Associated with IV Iron Products

- Arastu A et al. *JAMA Netw Open,* 2022
  - Examined results from >**35,000 doses** in **>12,000 patients**
  - Data were from chart reviews of practitioner observations **[not inferential surrogates from coding]**
  - **Concluded IV iron has exceedingly low risk of severe adverse reactions with near zero rate of epinephrine administration**

Arastu AH, et al. JAMA Netw Open. 2022

Comparative Risk of SAEs/Anaphylactic Reactions Associated with IV Iron Products

- Arastu A et al. *JAMA Netw Open,* 2022
  - **Premedication**, especially with diphenhydramine (often used as an inferential surrogate), is **associated with an increased risk of adverse events and worsened outcomes**
  - Intervention for minor infusion reactions should ***not*** be used as a surrogate for SAE/anaphylaxis

And this real-world patient video is why…

Arastu AH, et al. JAMA Netw Open. 2022

VIDEO

Inflammatory Bowel Disease (IBD)

In patients with IBD, oral iron therapy is associated with severe side effects, results in low iron absorption, has limited efficacy, and has been associated with worsening of the bowel symptoms

de Silva AD, et al. *Aliment Pharmacol Ther*. 2005;22:1097-1105.

Oral versus intravenous iron distinctly alters gut microbiota in IBD

Oral iron is standard but GI side effects and potential to exacerbate intestinal inflammation support implementation of IV iron

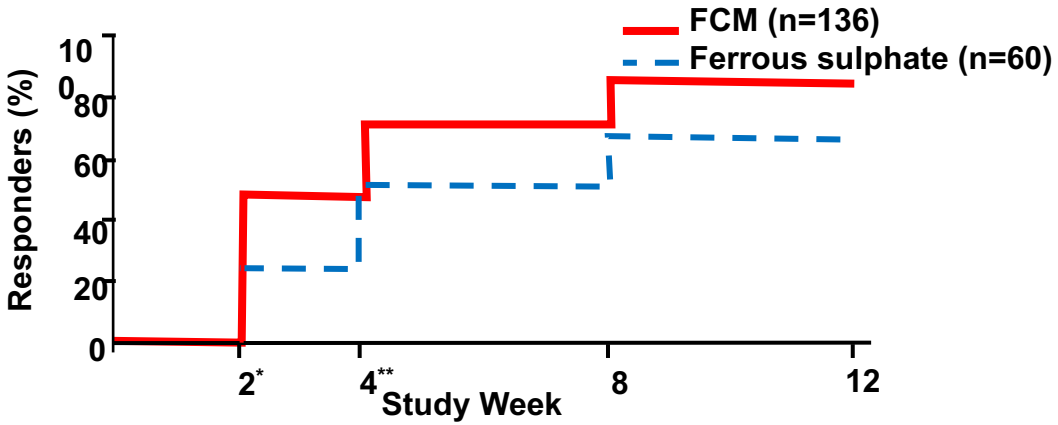
Oral and IV iron differentially affect bacterial communities and the metabolic landscape in IBD

IV iron might specifically benefit anemic patients with IBD with an unstable microbiota

Lee et al, GUT 2015

Ferric Carboxymaltose in IBD Patients

Significantly Faster Hb Response vs. Oral Iron
(Kaplan-Meier Analysis: Increase in Hb ≥2 g/dL at Weeks 2 and 4)



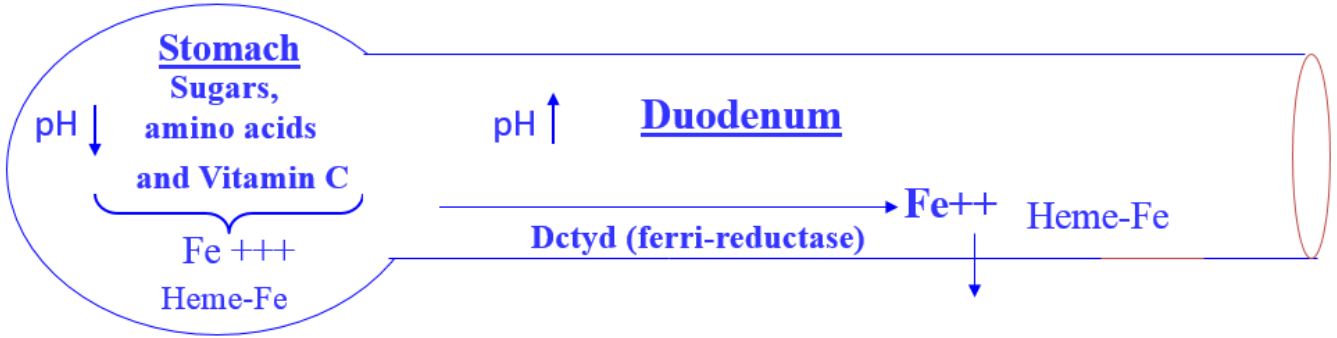
DOSING:

Ferric carboxymaltose: The median calculated iron deficit was 1405.5 mg (range 937–2102 mg), requiring 1–3 administrations on an individual basis at one week intervals.

Ferrous sulfate: 2x100 mg/day for 12 weeks (total 16,800 mg). Non-inferiority of ferric carboxymaltose confirmed in primary endpoint.

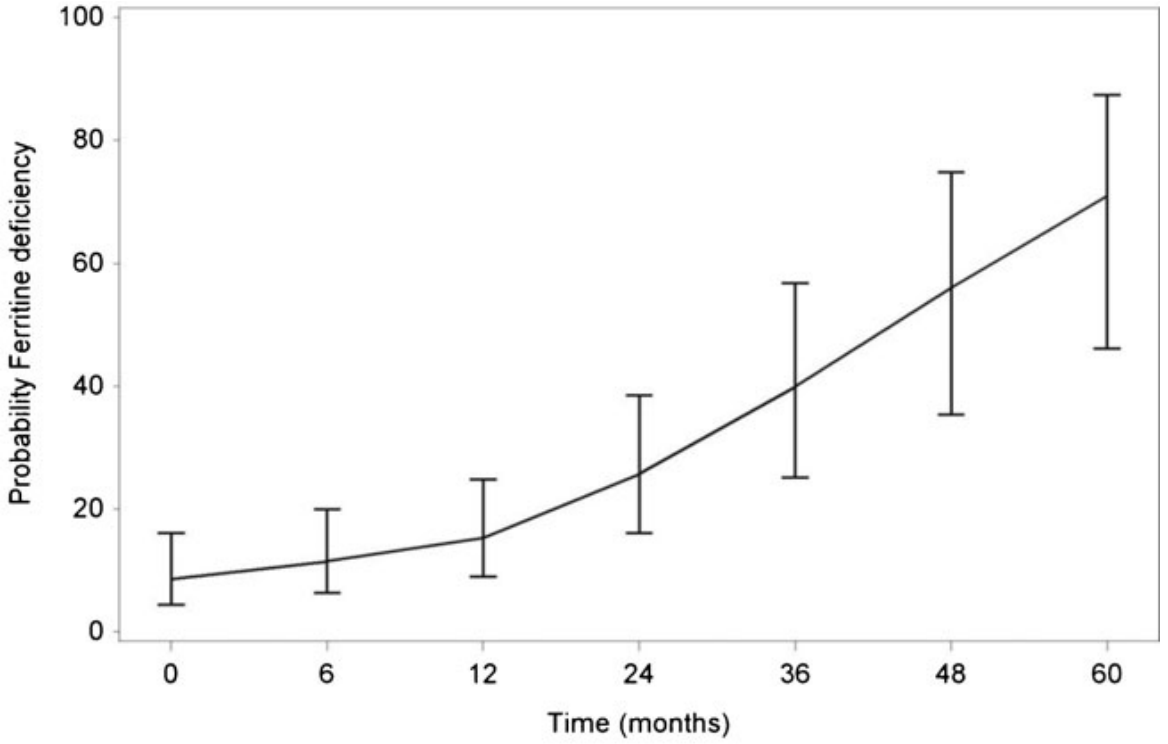
Treatment comparison log-rank test 0.009. **P*=0.0051; ***P*=0.0346.
Kulnigg S, et al. *Am J Gastroenterol*. 2008;103:1182-1192

Bariatric Surgery: Iron Absorption



With permission from Dr. Jerry Spivak, Johns Hopkins University School of Medicine

Predicted Probability of Ferritin Deficiency Over Time (with Indication of 95 % Confidence Interval)



Gesquiere et al, *Obesity Surgery* 2014;24:56-61

Change in Hemoglobin and Iron Parameters after Bariatric Surgery

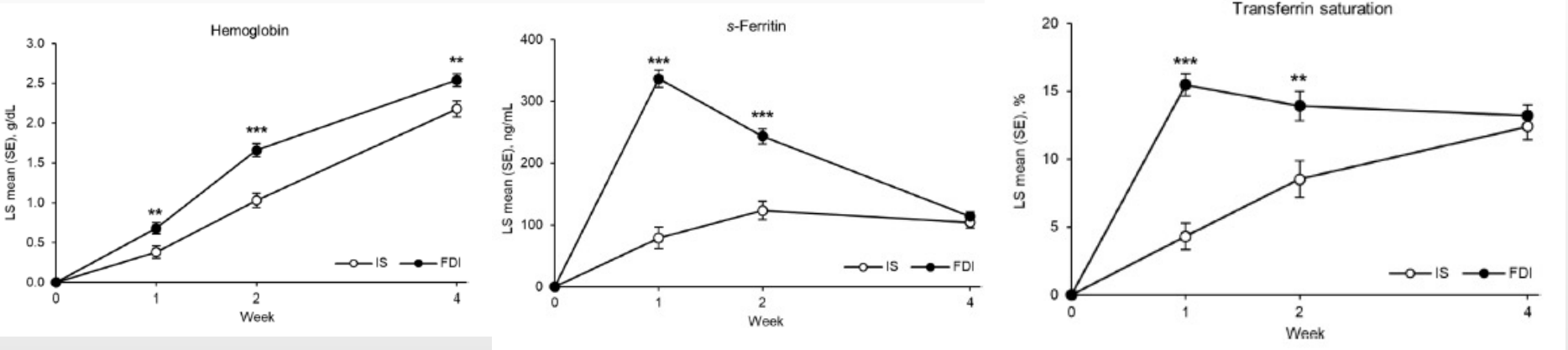
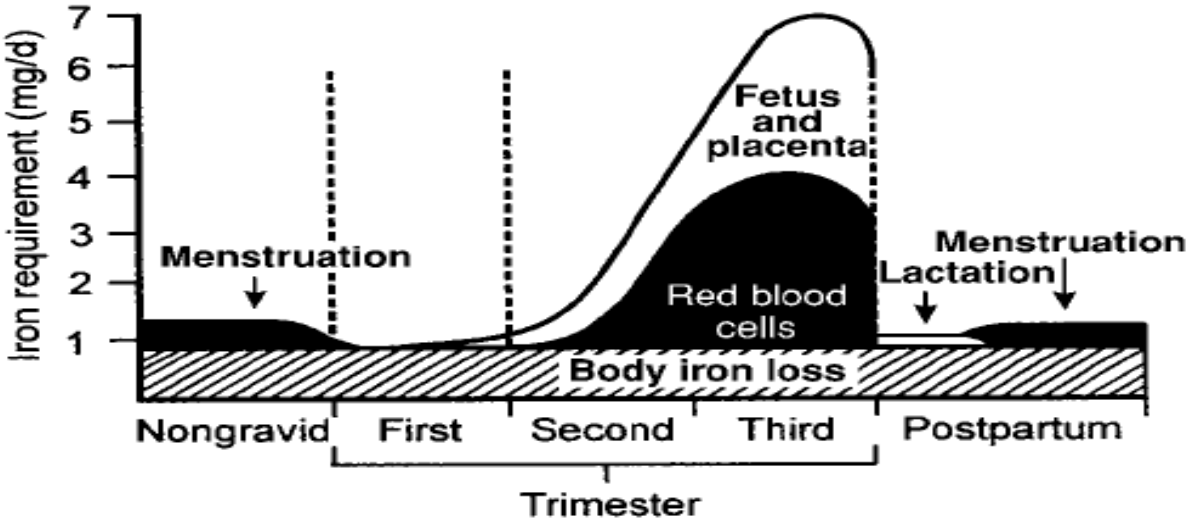


Fig. 1 LS mean change in hematological parameters from baseline over 4 weeks. **p<0.01, ***p<0.001 versus IS; estimates from mixed model for repeated measures with study, treatment and day as factors, treatment*day and baseline*day interactions, and baseline value as covariate. Data are presented for the FAS. FAS, full analysis set; FDI, ferric derisomaltose; IS, iron sucrose; LS, least squares; SE, standard error

Auerbach et al, Obesity Surgery, 2022

Daily Iron Requirement in Pregnancy



0.8mg/day 4-mg/day ~6mg/day

1st **2nd** **3rd**

Bothwell. Am J Clin Nutr 2000;72(suppl):257S-64S

Pregnancy

Maternal iron deficiency potentially affects fetal, neonatal, and childhood brain growth and development with adverse effects on myelination, neurotransmitters, and brain programming[1]

- Children born to iron-deficient mothers demonstrate lower cognitive function, memory, and motor development recognizable up to 19 years after iron repletion[2-4]

Iron deficiency anemia (IDA) in pregnancy has been associated with increased risk of adverse perinatal outcomes, including preterm birth, low birth weight, and small-for-gestational age infants[5-7]

1. Roncagliolo M, Walter T, Peirano P, et al. Am J Clin Nutr 1998;68:683–690
2. Congdon E, Westerlunjd B, Algarin C, et al. J Pediatr 2012;160:1227–1233
3. Chang S, Zeng L, Brouwer I, et al. Pediatrics 2013; 131:e755–e763
4. Tran T, Tran T, Simpson J, et al. BMC Pregnancy Childbirth 2014;14:8–18
5. Scholl T, Hediger M, Fischer R, et al. Am J Clin Nutr 1992;55:985–988
6. Ren A, Wang J, Ye R, et al. Int J Gynecol Obstet 2007;98:124–128.
7. Radlowski E, Johnson R. Front Human Neurosci 2013;7:585–592
8. Scholl T. Iron status during pregnancy: Am J Clin Nutr 2005;81:1218S–1222S. [PMID:15883455]

Fetal Iron Status with Maternal Iron Deficiency

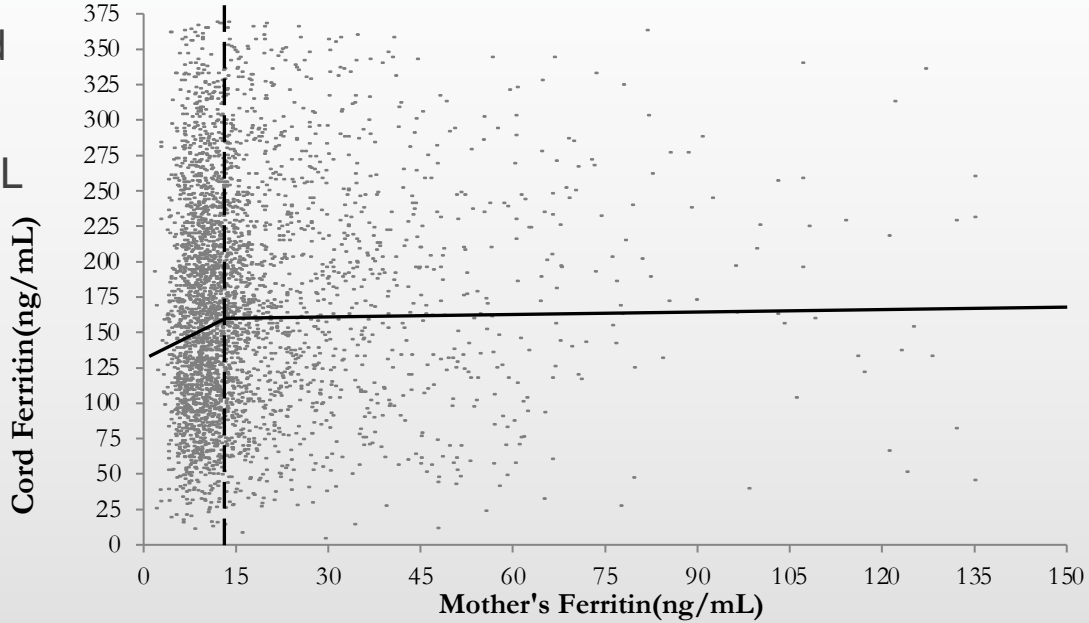
- Reduction in fetal iron status when maternal ferritin is <15 (Shao et al, J Nutrition 2012)
- Prenatal iron supplementation reduces maternal anemia, iron deficiency, iron deficiency anemia but iron deficiency is common in neonates even with iron supplementation (Zhou et al, J Nutrition 2015)

When Is Fetal Iron Status Compromised with Maternal Anemia?

Maternal Hgb < 85 g/L

Sliding scale between 85 and 105 g/L

Maternal Ferritin < 13.4 mcg/L



Shao et al, J. Nutrition, 2012

Infants at risk for neonatal iron deficiency

- From IRON DEFICIENT mothers OR those previously treated with IDA
- From mothers underweight or obese or with diabetes
- From Vegetarian mothers
- From multiparas
- From mothers with inflammatory bowel disease
- From mothers with HIV or smokers
- From mothers with inter-partum period of <6 months
- From mothers with history of abnormal uterine bleeding

TSAT and ferritin levels for all patients and for primigravida and multigravida patients.

	All patients N=102	Primigravida n=30	Multigravida n=72	P-value[1]
TSAT, mean (SD)	27.2 (14.2)	25.4 (15.6)	28.0 (13.6)	.39
TSAT, median (IQR)	23 (16, 38)	20.5 (15, 33)	24 (17, 39)	.22
Ferritin, mean (SD)	66.1 (43.6)	77.1 (56.1)	61.6 (36.7)	.17
Ferritin, median (IQR)	57.5 (36, 90)	68 (41, 94)	47 (35, 82.5)	.16
TSAT <19, n(%)	38 (37)	13 (43)	25 (35)	.41
Ferritin <20, n(%)	5 (5)	4 (13)	1 (1)	.02
Ferritin <25, n(%)	6 (6)	4 (13)	2 (3)	.06
Ferritin <30, n(%)	14 (14)	6 (20)	8 (11)	.24

Table 1.

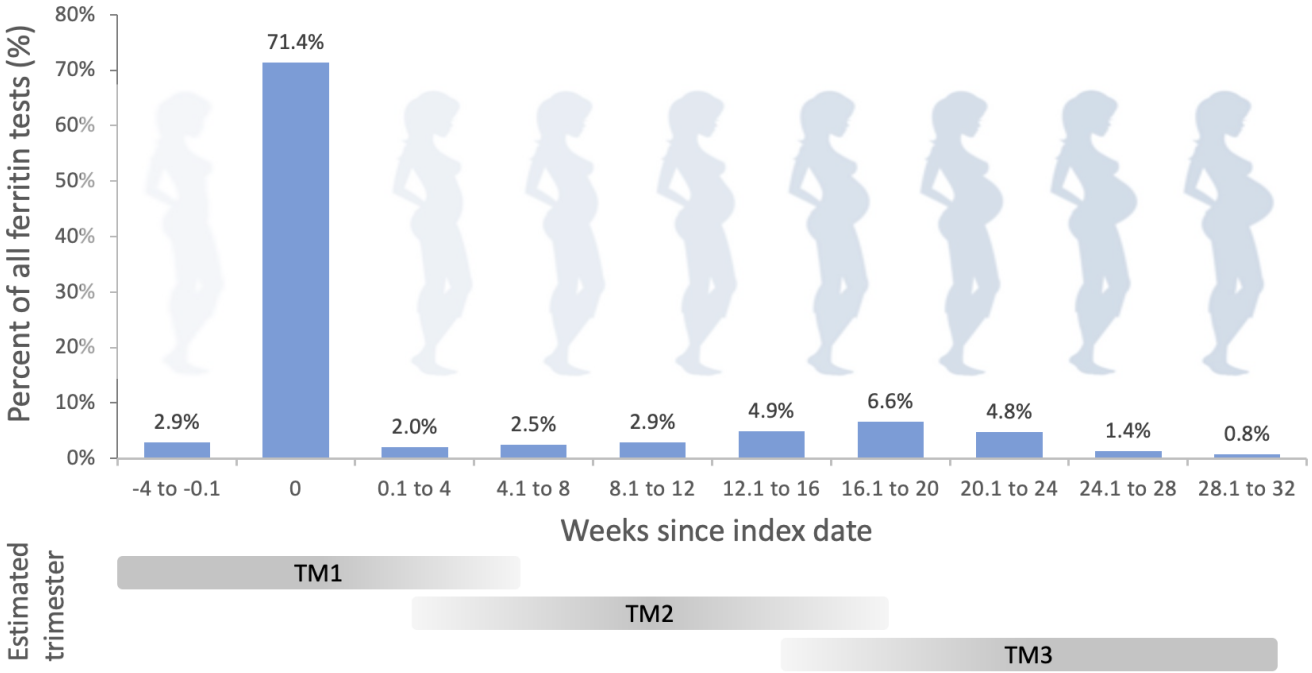
Auerbach et al, J Mat Fet Med, 2019

Results: Prevalence of ID

Iron Status (ferritin in µg/L)	Percent of women (n=25,880)
Ever normal (45-150)	45.6%
Ever iron insufficient (30-44.9)	25.2%
Ever iron deficient (<30)	52.8%
Ever severely iron deficiency (<15)	23.8%
Never iron deficient or insufficient (all ferritin levels 45-150)	30.2%

Teichman et al, *Blood Adv*, 2021

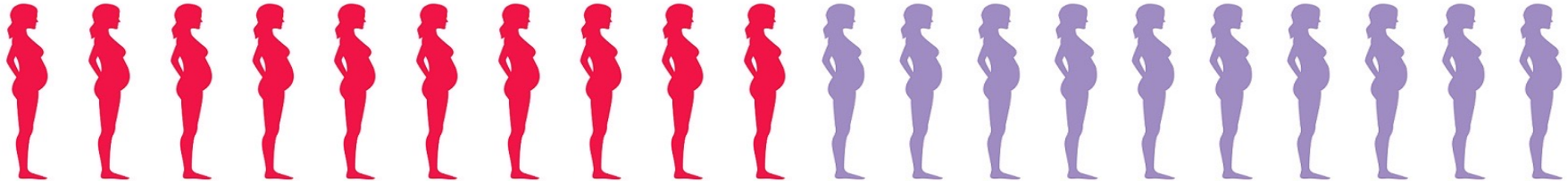
Results: When done, ID screening occurs early



Teichman et al,
Blood Adv., 2021

Conclusions

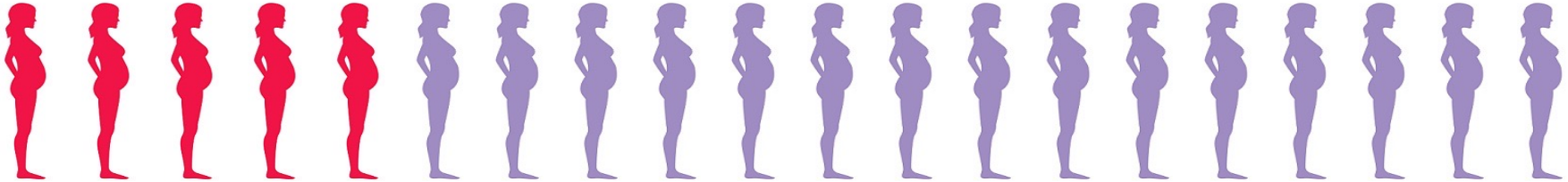
ID affects >50% of pregnancies in Ontario



Conclusions

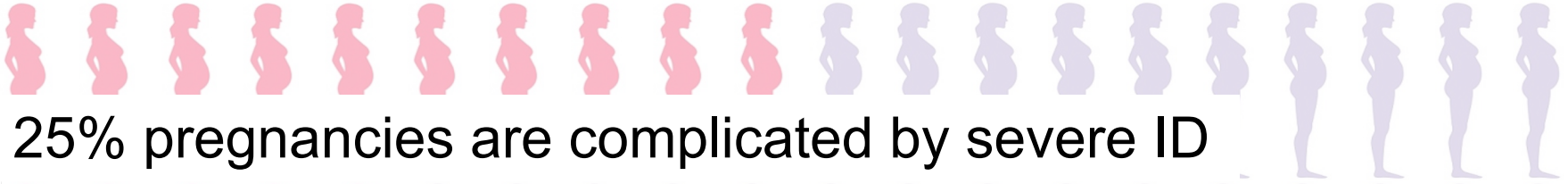
ID affects >50% of pregnancies in Ontario

25% pregnancies are complicated by severe ID



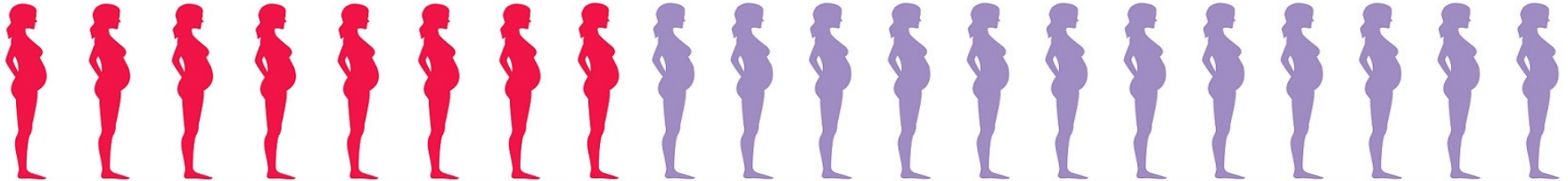
Conclusions

ID affects >50% of pregnancies in Ontario



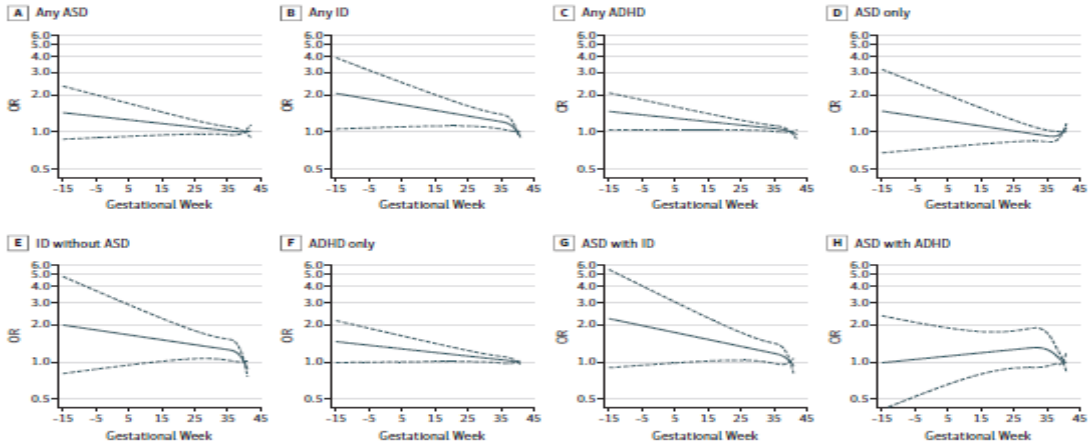
25% pregnancies are complicated by severe ID

Yet 40% pregnant women are not screened for ID



Association between gestational week of maternal anaemia diagnosis and offspring odds of neurodevelopmental outcomes among 29732 women with anaemia

Figure 2



The odds of each outcome according to gestational week at anemia diagnosis were flexibly fit using a restricted cubic spline model with 3 knots and gestational week 40 set as the referent. The solid line represents the odds ratio (OR) estimated from the fully adjusted generalized estimating equation model, clustered on maternal identifier, and adjusted for birth year, sex, educational level, disposable income, mother born outside Sweden, body mass index, maternal age, maternal psychiatric history, multiple birth, interpregnancy interval, and maternal infection during pregnancy. The dotted lines represent the 95% CI for the fully adjusted model. Results are shown for the potentially overlapping diagnostic outcomes (Figure 1B) in panels A to C and for the mutually exclusive diagnostic categories (Figure 1C) in panels D to H.

Abbreviations: ASD = Autism spectrum disorder; ADHD = Attention deficit hyperactivity disorder; ID= intellectual disability

Credit to: Wiegersma AM, Dalman C, Lee BK, Karlsson H, Gardner RM. Association of Prenatal Maternal Anemia With Neurodevelopmental Disorders. JAMA Psychiatry. 2019 Sep 18:1-12

Ferric carboxymaltose versus standard-of-care oral iron to treat second-trimester anaemia in Malawian pregnant women: a randomised controlled trial

Sant-Rayn Pasricha, Martin N Mwangi, Ernest Moya, Ricardo Ataide, Glory Mzembe, Rebecca Harding, Truwah Zinenani, Leila M Larson, Ayse Y Demir, William Nkhono, Jobiba Chinkhumba, Julie A Simpson, Danielle Clucas, William Stones, Sabine Braat, Kamija S Phiri

- Design: Open-label, individually randomized controlled trial
- Inclusion: singleton pregnancy of 13–26 weeks' gestation, Hb <10.0 g/dL and negative malaria rapid diagnostic test
- Treatment: FCM up to 1000 mg at enrolment vs. standard of care (60 mg elemental iron twice daily for 90 days)
- Primary outcomes: maternal anemia at 36 weeks' gestation and neonatal birthweight

	Ferric carboxymaltose (n=430)	Standard of care (n=432)	Prevalence ratio (95% CI)	Mean difference (95% CI)	Geometric mean ratio (95% CI)	p value
Primary outcome						
Anaemia at 36 weeks' gestation	179/341 (52%)	189/333 (57%)	0·92 (0·81 to 1·06)	..	..	0·27
Key secondary outcomes						
Moderate–severe anaemia at 36 weeks' gestation	67/341 (20%)	82/333 (25%)	0·81 (0·61 to 1·07)	..	..	0·14
Hb change from baseline at 36 weeks' gestation, g/dL	2·02 (1·41)	1·85 (1·49)	..	0·15 (–0·02 to 0·33)	..	0·077
Median ferritin change from baseline at 36 weeks' gestation (IQR), µg/L	59·20 (28·20–125·60)	22·30 (14·20–35·10)	..	..	2·55 (2·28 to 2·86)	<0·0001*
Iron deficient at 36 weeks' gestation	60/336 (18%)	142/341 (42%)	0·4 (0·33 to 0·55)	..	..	<0·0001*
Iron deficient anaemia at 36 weeks' gestation	29/324 (9%)	93/321 (29%)	0·30 (0·20 to 0·44)	..	..	<0·0001*

Pasricha et al. Lancet 2023; 401: 1595–609

Ferric Carboxymaltose Versus Oral Iron to Treat Second-trimester Anaemia in Malawian Pregnant Women: A Randomised Controlled Trial

- IV iron markedly reduces IDA compared with oral iron
- Effect lasts through duration of pregnancy into the post-partum
- Hemoglobin elevation was more rapid with IV iron

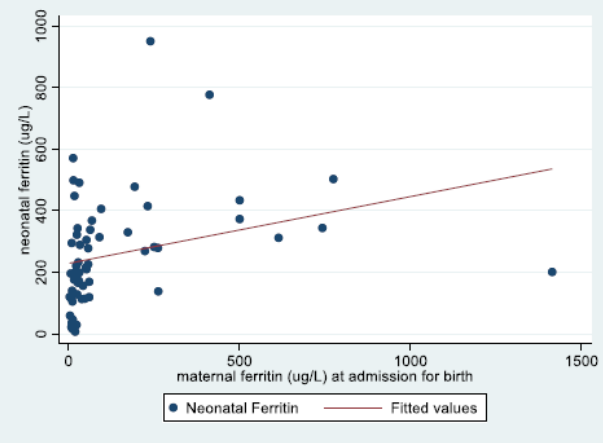
Pasricha et al, Lancet 2023

Neonatal outcomes from a randomized controlled trial of maternal treatment of iron deficiency anemia with intravenous ferumoxytol vs oral ferrous sulfate

Adeola M. Awomolo, MD; Amanda McWhirter, MD; Lynn C. Sadler, MBChB, MPH; Lynn M. Coppola, MD, MPH; Meghan G. Hill, MBBS, MS

- RCT including 124 participants with anemia
- Treatment: 1:1 ratio to either 510 mg x2 ferumoxytol or 325 mg oral ferrous sulfate twice daily

FIGURE 2
Neonatal ferritin by maternal ferritin with regression line



Awomolo. Cord blood iron indices after maternal ferumoxytol infusions. Am J Obstet Gynecol MFM 2023.

Result:
- Higher cord blood ferritin in infants of participants treated with ferumoxytol (294 vs 186, P=.005)
- Equivalent iron (158 vs 146, P=.4), transferrin (186 vs 196, P=.4), and total iron binding capacity in infants of participants treated with ferumoxytol (246 vs 244, P=1)

Awomolo et al. Am J Obstet Gynecol MFM 2023;5:101063

Intravenous Iron Compared With Oral Iron Supplementation for the Treatment of Postpartum Anemia

A Randomized Controlled Trial

Makenzie Kothmann
Rachel Stepanek

Mentor: Antonio Saad

Saad et al, Obs and Gynecol, 2023

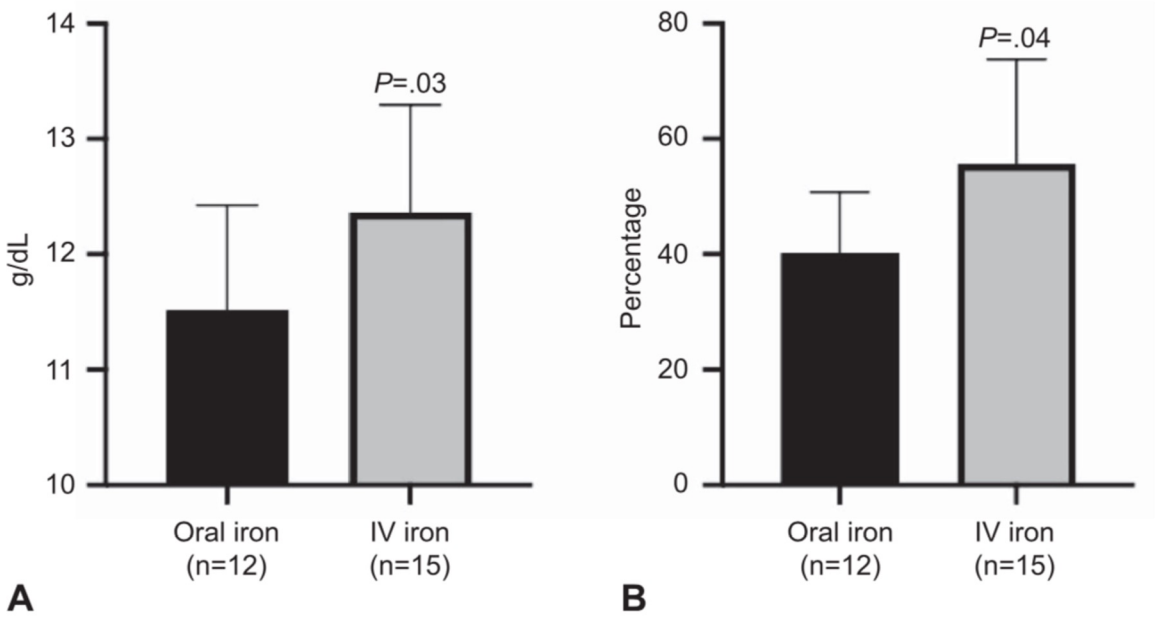


Fig. 1. Hemoglobin level (**A**) and percent increase in hemoglobin level (**B**) at least 6 weeks postpartum. IV, intravenous.

Saad. Intravenous Iron for the Treatment of Postpartum Anemia. Obstet Gynecol 2023.

Pregnancy: Treatment options

Oral iron

Up to 70% to whom oral iron is prescribed report gastrointestinal distress[1,2]

A study of adherence and side effects of three ferrous sulfate regimens in anemic pregnant women in clinical trials concluded the incidence of gastrointestinal side effects was unacceptably high[3,4]

Intravenous iron

- Numerous publications report the safety and efficacy of IV iron during pregnancy but its use is sporadic[5]
- No IV formulation had been assigned Pregnancy Category A by the Food and Drug Administration
- Excessive fears of anaphylactic reactions
- Misperception among clinicians that the incidence and severity of infusion reactions is unacceptably high[6]

1. Souza A, Batista F, Bresani C. Cad Saude Publica 2009;6:1225–1233
2. Tolkien Z, Stecher L, Mander A, et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: A systematic review and meta-analysis. PLoS One 2015;10:e0117383. DOI:10.1371/journal.pone.0117383.
3. Van Wyck D, Martens M, Seid M, et al. Obstet Gynecol 2007;110:267–278
4. Dhanani J, Ganguly B, Chauhan L. J Pharmacol Pharmcother 2012;3:314–319
5. American College of Obstetricians and Gynecologists. ACO Practice Bulletin No. 95: Anemia in pregnancy. Obstets Gynecol 2008;112:201–207
6. Auerbach M, Ballard H, Glaspy J. Lancet 2007;369:1502–1504

Discussion

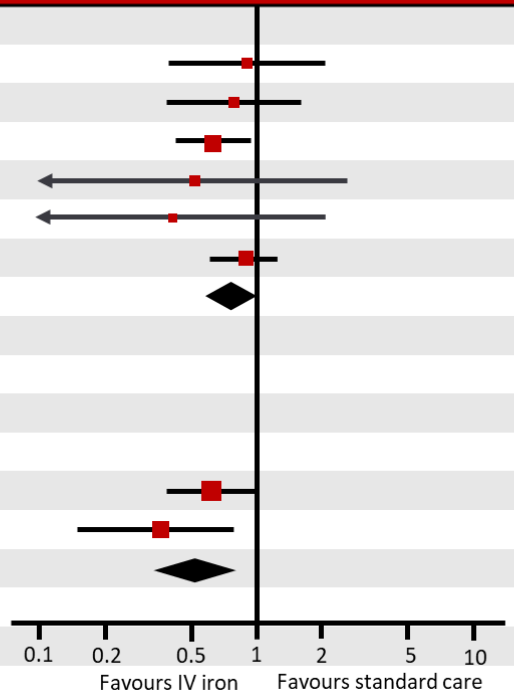
- The results support the convenience, safety, and efficacy of a single infusion of a gram of intravenous iron as therapy for iron deficiency
- We believe IV iron should be administered as soon as oral iron intolerance occurs or as front line therapy to those in whom oral iron is known to be ineffective or harmful such as after bariatric surgery or IBD. IV, and not oral iron, should be administered for IDA of pregnancy if Hb<10 g/dL in the second trimester and to all after week 30. If oral iron is indicated, one tablet QOD is the preferred schedule. Oral iron should be proscribed in the 3rd trimester
- All pregnant women should be screened for ID at presentation to their obstetricians and again at the beginning of the third trimester (week 30)
- All at risk newborns screened for ID at birth and treated if deficient
- Compared to oral iron, intravenous iron has fewer side effects and nearly always effective. Our data and that of others call for large prospective studies of IV vs. oral iron for therapy of maternal iron deficiency anemia

Auerbach et al, AJM 2017; 130:1402-1407

IV Iron in Cancer

Clinical Trial Evidentiary Base

Study or Subcategory	IV Iron n/N	Standard Care n/N	Risk Ratio (fixed) 95% CI	Weight %	Risk Ratio (fixed) 95% CI
01 Trials of CIA with ESA					
Auerbach 2004	9/78	10/79		7.64	0.91 (0.39–2.12)
Henry 2007	11/63	14/63		10.77	0.79 (0.39–1.60)
Bastit 2008a	32/200	49/196		38.07	0.64 (0.43–0.95)
Beguin 2008	2/50	4/52		3.02	0.52 (0.10–2.71)
Pedrazzoli 2008	2/73	5/76		3.77	0.42 (0.08–2.08)
Auerbach 2010	42/116	49/122		36.74	0.90 (0.65–1.25)
Subtotal (95% CI)	580	588		100.00	0.76 (0.61–0.95)
Total events	98	131			
Test for heterogeneity: $Chi^2 = 2.70$; df = 5 (P=0.75); $I^2 = 0\%$					
Test for overall effect: Z = 2.38 (P=0.02)					
02 Trials of CIA without ESA					
Kim 2007	12/30	29/46		62.37	0.62 (0.38–1.01)
Dangsuwan 2010	5/22	14/22		37.63	0.36 (0.16–0.82)
Subtotal (95% CI)	52	67		100.00	0.52 (0.34–0.80)
Total events	17	43			
Test for heterogeneity: $Chi^2 = 1.28$; df = 1 (P=0.26); $I^2 = 21.9\%$					
Test for overall effect: Z = 3.02 (P=0.002)					

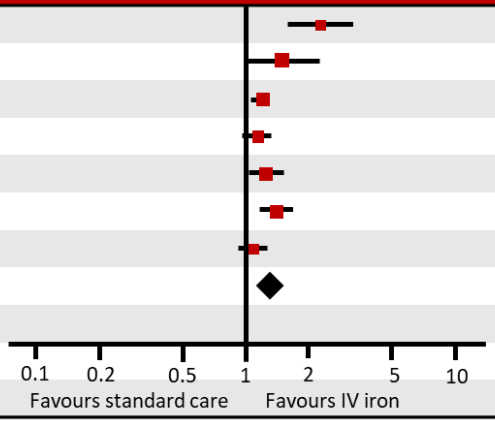


Gafter-Gvili A, et al. *Acta Oncol*. 2013.

Studies of ESA +/- IV Iron in Oncology

Hematopoietic Response

Study or Subcategory	IV Iron n/N	Standard Care n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Auerbach 2004	53/78	24/79		8.11	2.24 (1.55–3.23)
Henry 2007	32/60	21/59		6.81	1.50 (0.99–2.27)
Bastit 2008	172/200	143/196		20.58	1.18 (1.06–1.31)
Beguin 2008	46/50	42/52		17.57	1.14 (0.97–1.33)
Pedrazzoli 2008	56/73	46/76		13.94	1.27 (1.02–1.58)
Auerbach 2010	86/116	65/122		15.18	1.39 (1.14–1.70)
Steensma 2010	114/164	106/163		17.81	1.07 (0.92–1.24)
Total (95% CI)	741	747		100.00	1.28 (1.12–1.45)
Total events	559	447			
Test for heterogeneity: $Chi^2 = 18.81$; df = 6 (P=0.005); $I^2 = 68.1\%$					
Test for overall effect: Z = 3.72 (P=0.0002)					



Gafter-Gvili A, et al. *Acta Oncol.* 2013.

Restless leg syndrome (RLS)

- Thought to be related to low brain iron despite normal serum iron levels

- Affects 35 % – 50% of people with iron deficiency

- Open- label studies have shown IV iron replacement improves RLS No randomized double blind controlled trials evaluating IV vs. oral iron

Short V, et al. AJH. 2023.

A randomized double-blind pilot study to evaluate the efficacy, safety, and tolerability of intravenous iron versus oral iron for the treatment of restless legs syndrome in patients with iron deficiency anemia

Inclusion Criteria

- Aged ≥18 years.
- Diagnosis of RLS based on Cambridge–Hopkins diagnostic questionnaire and confirmed by HTDI.
- International RLS Study Group Severity Scale (IRLSS) score >15
- IDA defined as either ferritin <20 µg/L or transferrin saturation
- (TSAT) <19%, with a hemoglobin <13 g/dL for both males and females
- Women had to be surgically sterile, post-menopausal, or on contraceptive

Short V, et al. AJH. 2023.

A randomized double-blind pilot study to evaluate the efficacy, safety, and tolerability of intravenous iron versus oral iron for the treatment of restless legs syndrome in patients with iron deficiency anemia

- **N = 100**
- **Randomized 1:1 Ferumoxytol or oral iron**

- **Co-primary Outcomes**
  - CGI-I score at Week 6
  - change from baseline in IRLSS score at Week 6

- **Secondary Outcome**
  - Change from baseline in the PGI-S at Week 6

TABLE 1 Baseline demographics and clinical characteristics.

	IV iron $n = 48$	Oral iron $n = 46$	p-Value[a]
Age, years	48.8 (15.8)	49.5 (16.6)	.80
Female	87.5	91.3	.54
Hemoglobin, g/dL	11.3 (1.3)	10.8 (1.6)	.14
MCV, fL	82.2 (7.8)	79.2 (9.9)	.015
Ferritin, µg/L	22.6 (19.6)	13.5 (12.1)	.17
TSAT, %	11.4 (5.9)	9.5 (6.5)	.025
Iron, µg/dL	42.5 (18.7)	41.0 (30.1)	.11
TIBC, µg/dL	385.9 (74.5)	411.9 (61.5)	.09
IRLSS score	21.9 (5.9)	21.8 (8.0)	.96
PGI-S score	4.2 (1.2)	4.3 (1.4)	.67

CGI- I, Clinician Global Impression—Improvement
IRLSS, International RLS Study Group Severity
PGI-S, Patient Global Inventory—Severity;

Short V, et al. AJH. 2023.

No difference in CGI-I, IRLSS and PGI-S between IV and oral at week 6

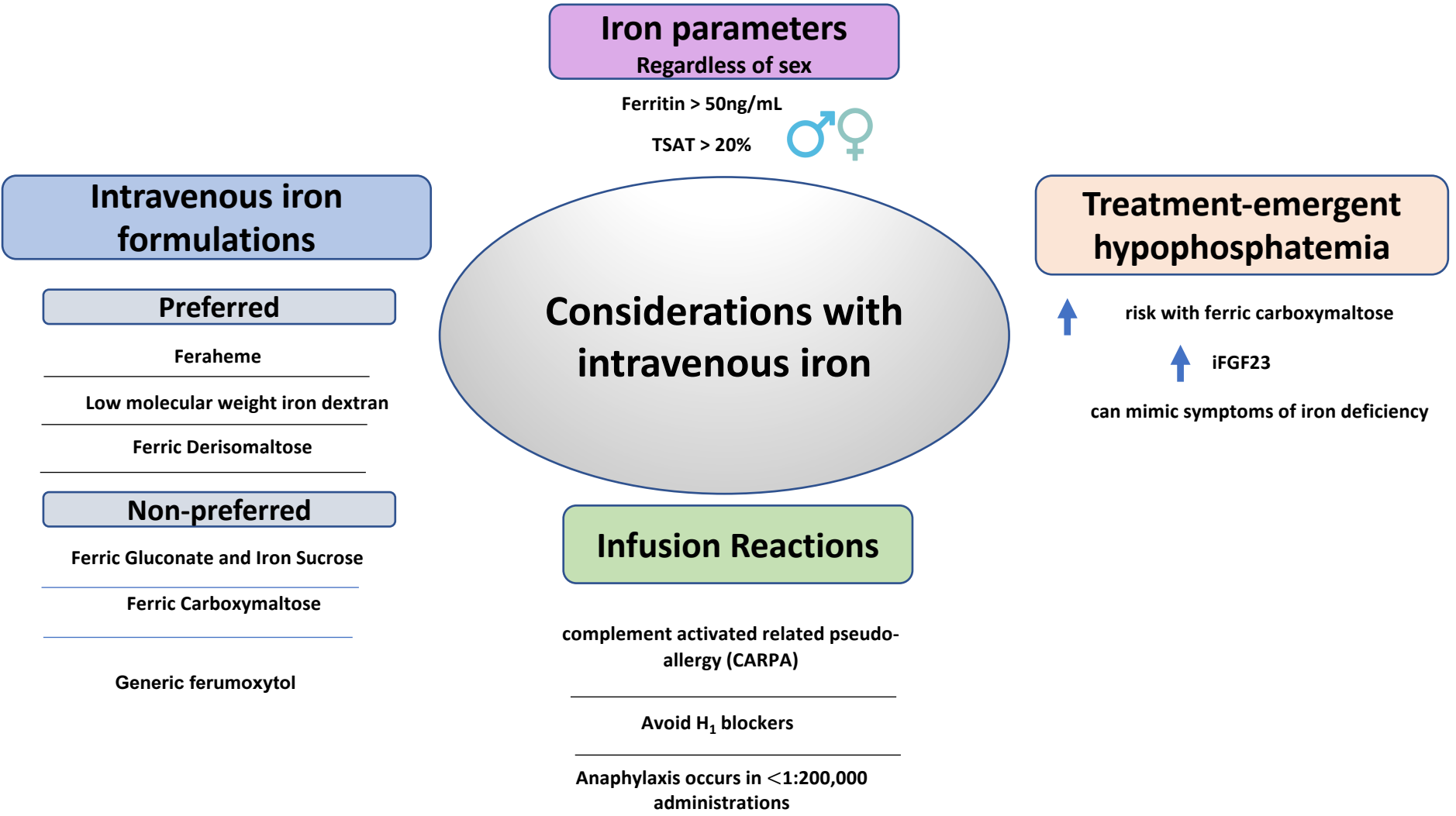
	IV iron mean (SD)	Oral iron mean (SD)	*p*-Value[a]
Change in IRLSS score	$n = 48$	$n = 46$	.27
	−7.9 (8.7)	−10.1 (10.4)	
CGI-I score at Week 6	$n = 28$	$n = 28$	.70
	2.0 (1.2)	1.9 (1.3)	
Change in PGI-S score	$n = 30$	$n = 27$	.35
	−1.7 (1.8)	−2.1 (1.8)	
Change in hemoglobin, g/dL	$n = 36$	$n = 32$	.22
	1.2 (1.3)	1.7 (1.8)	
Change in MCV, fL	$n = 36$	$n = 33$	.10
	4.0 (5.9)	6.5 (6.4)	
Change in iron, µg/dL	$n = 35$	$n = 31$	.87
	36.8 (21.8)	35.3 (50.3)	
Change in ferritin, µg/L	$n = 34$	$n = 33$	<.0001
	200.3 (133.0)	23.3 (21.2)	
Change in TSAT, %	$n = 35$	$n = 33$	.17
	16.5 (7.5)	12.2 (16.3)	
Change in TIBC, µg/dL	$n = 35$	$n = 32$	.004
	−105.7 (60.4)	−64.3 (52.5)	

Greater GI adverse events were seen in those who received oral iron.

Short V, et al. AJH. 2023.

CONSENSUS RECOMMENDATIONS
Formulations administered as a single TDI is recommended over formulations requiring multiple dose infusions
Optimal Formulations for TDI: ferumoxytol, LMWID, FDI **Suboptimal Formulations for TDI:** ferumoxytol generic, FCM, IS, FG
Administer Ferumoxytol as a TDI of 1020mg in 30 minutes
Pregnancy: Avoid IV iron prior to 13 weeks gestation. Recommend against fetal monitoring during and following IV iron administration
Monitoring for 30 minutes post- IV iron administration is not indicated
Premedication should be reserved for those persons at high risk of HSRs
Allow 30 minutes between administration of IV iron & other medications* at high risk for HSRs.
Ferritin goal of 50 ng/mL regardless of sex at birth
Manage infusion reactions as outlined in Figure 2
Rechallenge with the same IV iron formulation may be attempted following an infusion reaction
Phosphorus monitoring following IV iron administration should be guided by clinical symptoms for all formulations exc FCM**
Management of treatment-emergent hypophosphatemia is directed at preventing secondary hypoparathyroidism

Clinical Pearls
Ferumoxytol can be infused at 1020mg in 30 minutes.
Monitoring for 30 minutes after IV iron administration is not required.
Premedication should be reserved for those patients at high risk of HSRs.
Rechallenge with the same formulation may be attempted following an infusion reaction.
Phosphorus monitoring following FCM administration should be standard practice
Management of treatment-emergent hypophosphatemia is directed at preventing secondary hypoparathyroidism


Iron parameters
Regardless of sex
Ferritin > 50ng/mL
TSAT > 20%
Intravenous iron formulations
Preferred
Feraheme
Low molecular weight iron dextran
Ferric Derisomaltose
Non-preferred
Ferric Gluconate and Iron Sucrose
Ferric Carboxymaltose
Generic ferumoxytol
Considerations with intravenous iron
Infusion Reactions
complement activated related pseudo-allergy (CARPA)
Avoid H1 blockers
Anaphylaxis occurs in <1:200,000 administrations
Treatment-emergent hypophosphatemia
risk with ferric carboxymaltose
iFGF23
can mimic symptoms of iron deficiency

Take home messages

- Severe infusion reactions to IV iron are **vanishingly rare**
- Fishbane/CARPA reactions occur but can easily be managed by pausing the infusion and rechallenge the patient without additional treatment once the symptoms have disappeared
- Only head-to-head randomized clinical trials powered to show a relative difference between IV iron formulations are reliable as studies using surrogates miss inappropriate intervention for the reaction you just witnessed.
- The use of ferric gluconate or iron sucrose for outpatient treatment of iron deficiency should be proscribed