Treatment of Iron Deficiency: A New Paradigm

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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

Use 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

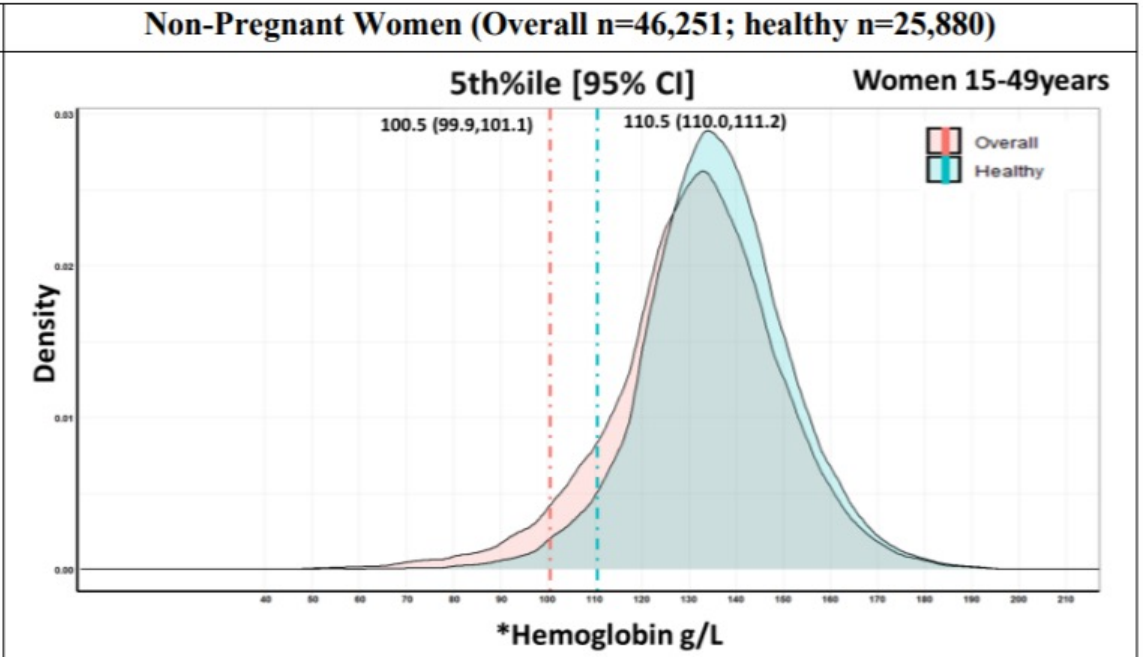


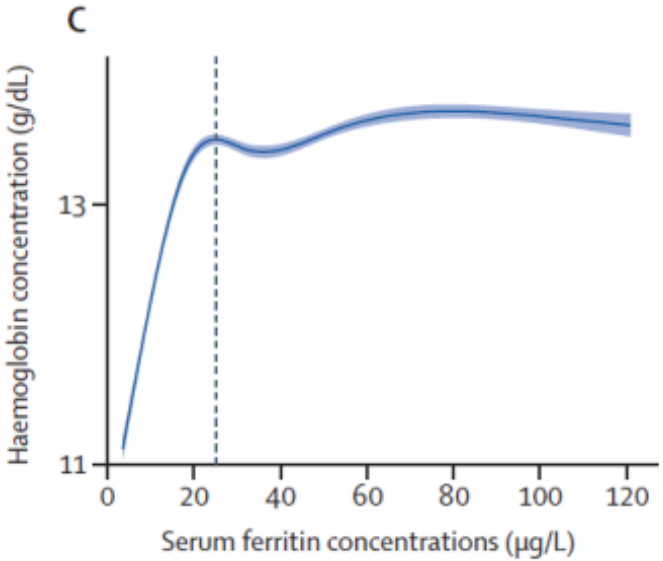
Table 1. Descriptive Characteristics and Prevalence of Selected Biological Indicators Among the Total Sample and Apparently Healthy Subsample in a Multinational Sample

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)

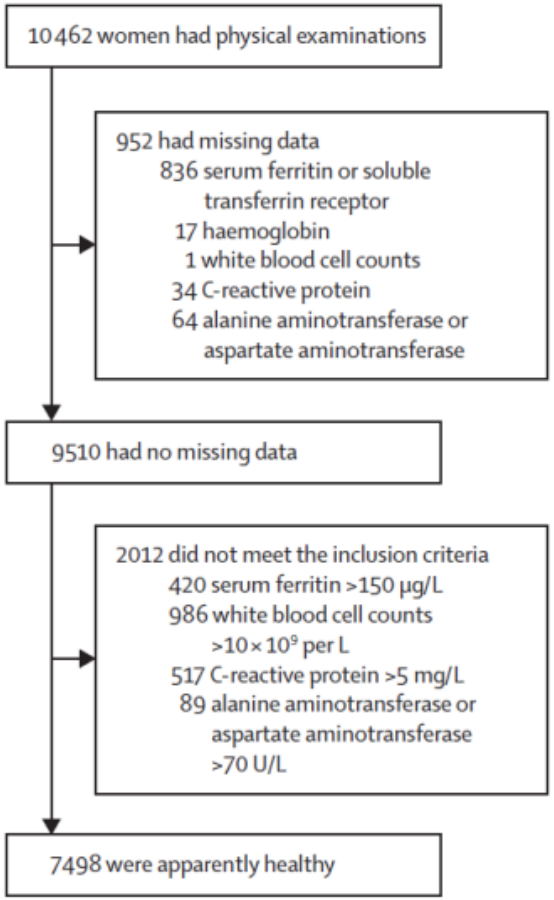
Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional study

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

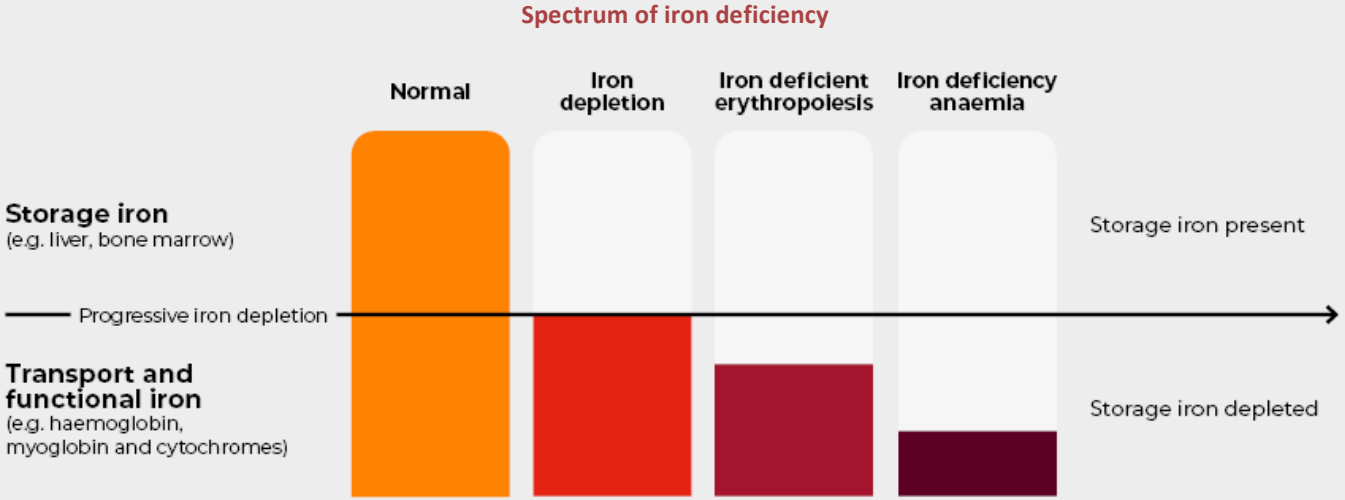
www.thelancet.com/haematology Vol 8 August 2021



Ferritin 25.2 (24.2-26.2)



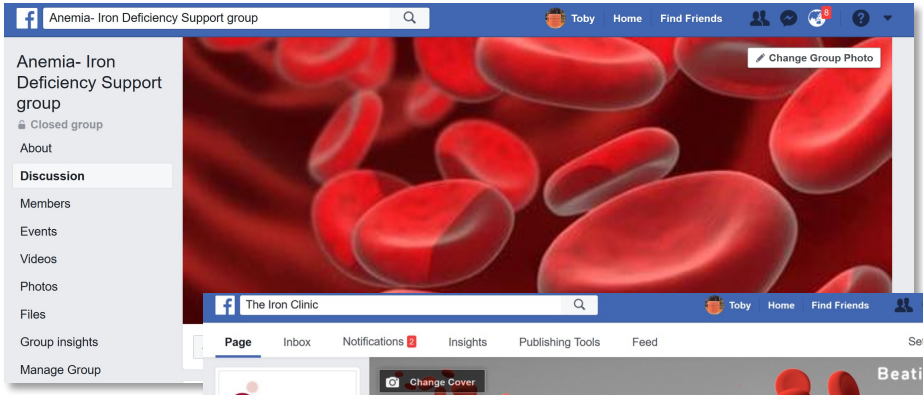
Iron deficiency is the disease

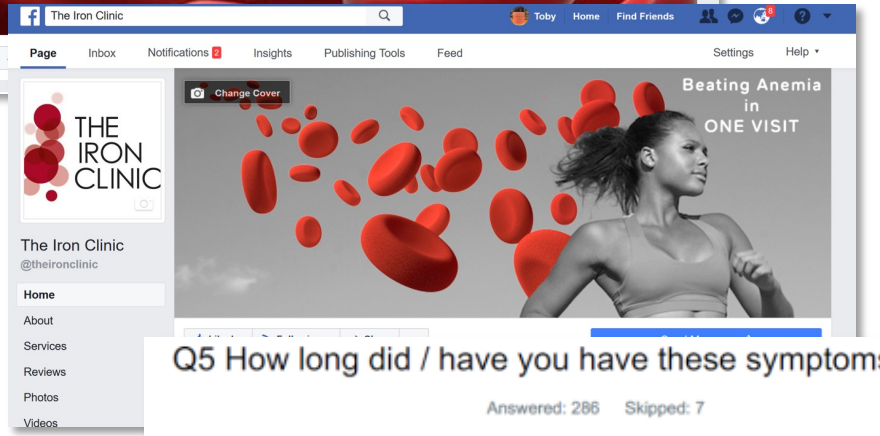


Modified with permission from Sarah Cusick PhD, Centers for Disease Control and Prevention.

Example of laboratory profile				
Serum ferritin (µg/L)	60	<15	<15	<15
Transferrin saturation (%)	35	35	<15	<15
Haemoglobin (g/L) – female	>120	>120	>120	<120
Haemoglobin (g/L) – male	>130	>130	>130	<130

Australian Red Cross. https://transfusion.com.au/anaemia_management/iron_deficiency_without_anaemia


Anemia- Iron Deficiency Support group
Toby
Home
Find Friends
Anemia- Iron Deficiency Support group
Closed group
About
Discussion
Members
Events
Videos
Photos
Files
Group insights
Manage Group
Change Group Photo


The Iron Clinic
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Find Friends
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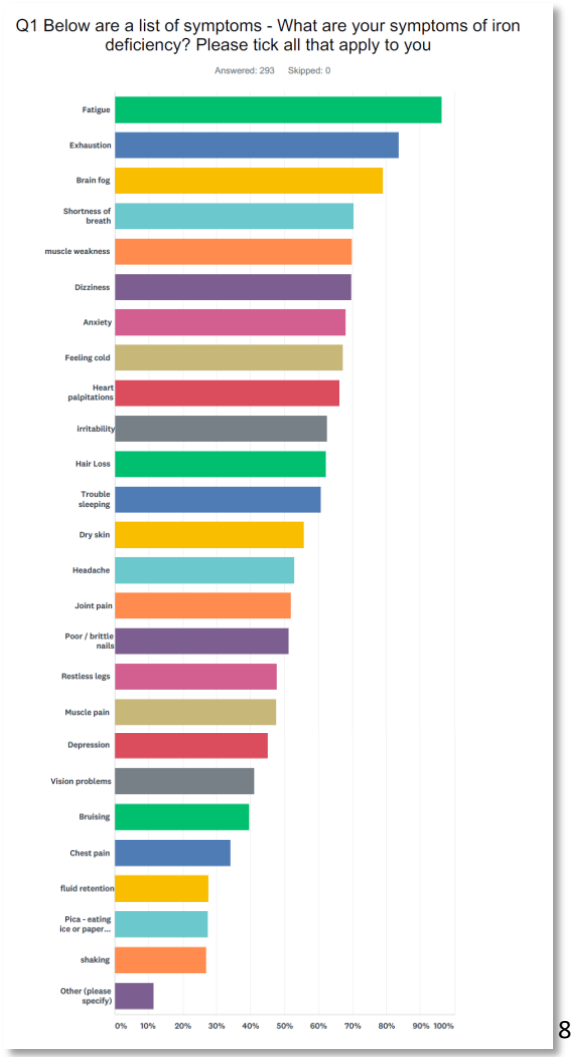
Inbox
Notifications 2
Insights
Publishing Tools
Feed
Settings
Help
THE IRON CLINIC
The Iron Clinic
@theironclinic
Home
About
Services
Reviews
Photos
Videos
Change Cover
Beating Anemia in ONE VISIT

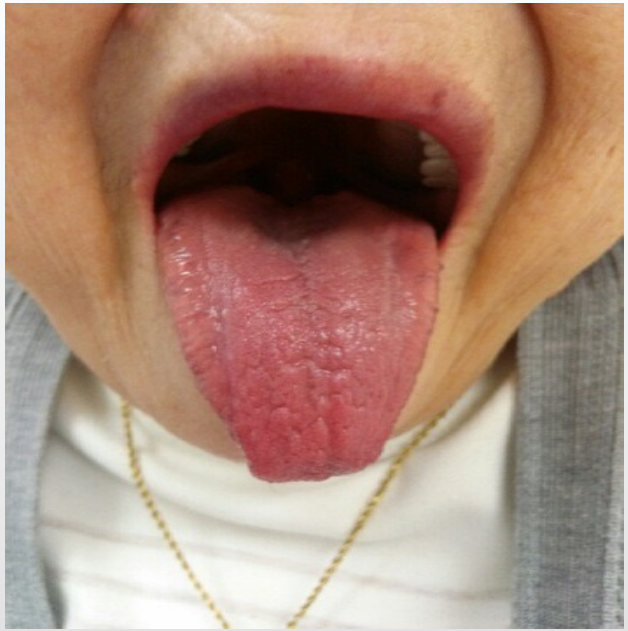

Q5 How long did / have you have these symptomsYEARS
Answered: 286
Skipped: 7
0
1
2
3
4
5
6
7
8
9
10


Q1 Below are a list of symptoms - What are your symptoms of iron deficiency? Please tick all that apply to you
Answered: 293
Skipped: 0
Fatigue
Exhaustion
Brain fog
Shortness of breath
muscle weakness
Dizziness
Anxiety
Feeling cold
Heart palpitations
irritability
Hair Loss
Trouble sleeping
Dry skin
Headache
Joint pain
Poor / brittle nails
Restless legs
Muscle pain
Depression
Vision problems
Bruising
Chest pain
fluid retention
Pica - eating ice or paper...
shaking
Other (please specify)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

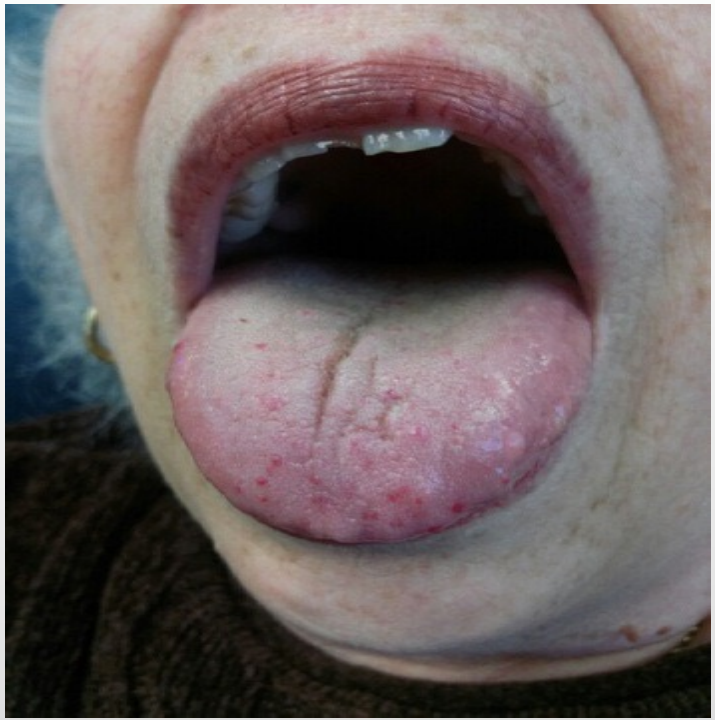
Symptoms of Iron Deficiency

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

Pretreatment Tongue



Healed Tongue



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.

IV Iron Dosing

Formulation	Approved Dosing	Maximum Safe Dose
LMW Iron dextran	100mg over 2 min	TDI over 1-4 hours [1-2]
Ferumoxytol (US only)	510mg in 15 min	510mg over 90-180 seconds or 1020mg over 15-30 min [3]
Ferric carboxymaltose (FCM)	750mg over 15 min	1000mg over 15 min [4]
Ferric derisomaltose	20mg/kg over 15 min <1000mg and 60 min for >1000	2000mg over 60 min [5,6]

1.Auerbach et al. Am J Kidney Dis. 1998;31:81-86.
2.Auerbach et al. Presented at American Society of Hematology, December 2009, New Orleans, LA.
3.Ferumoxytol [prescribing information]. Lexington, MA: AMAG Pharmaceuticals, Inc; 2009.
4.FCM [summary of product characteristics]. France: Vifor Pharma; 2009.
5.Iron isomaltoside [summary of product characteristics]. Denmark: Pharmacosmos; 2010.
6.Dahlerup et al. Scand of Gastroenterol 2016;21:1-7

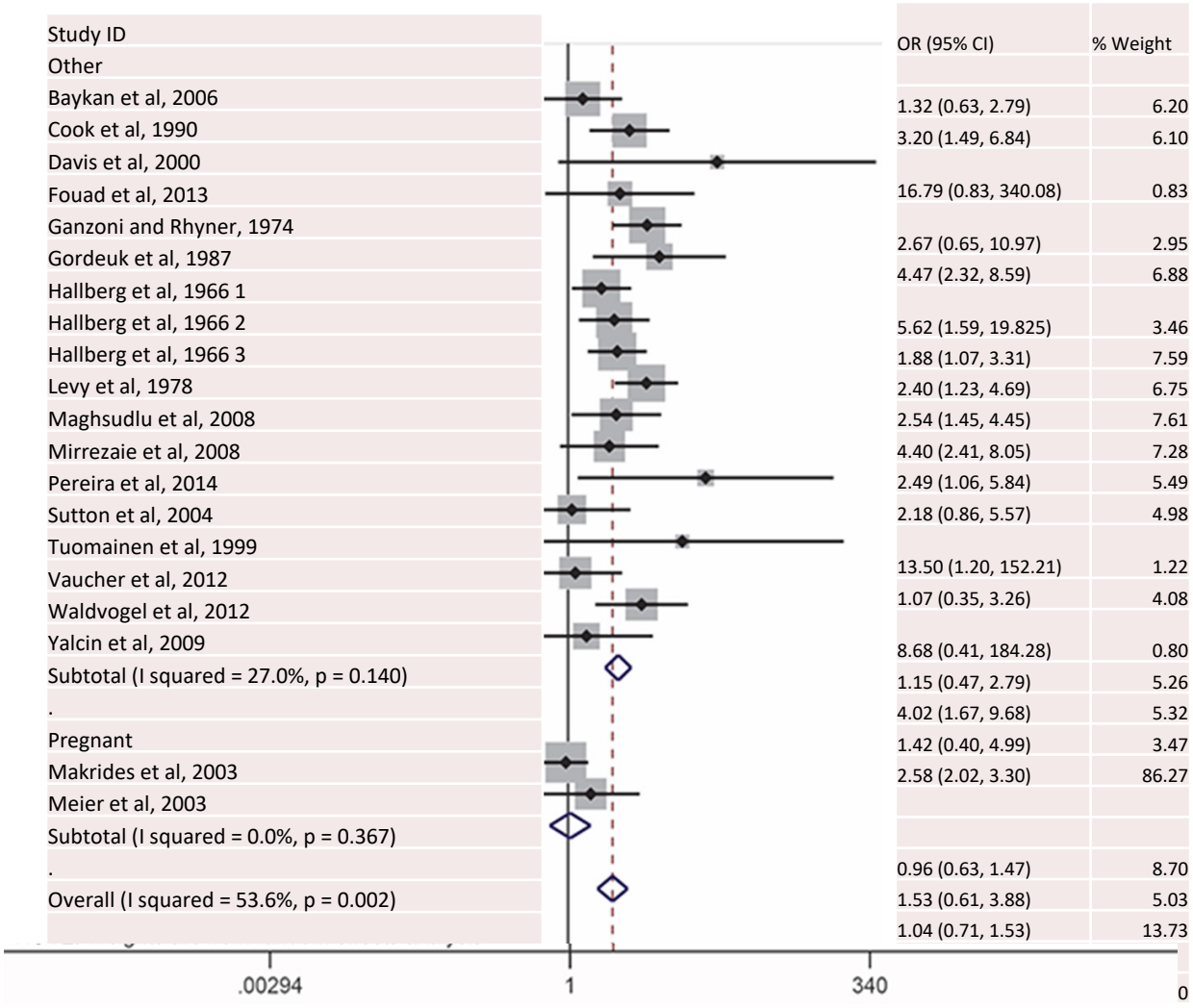
Adverse Events with Iron Supplementation

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

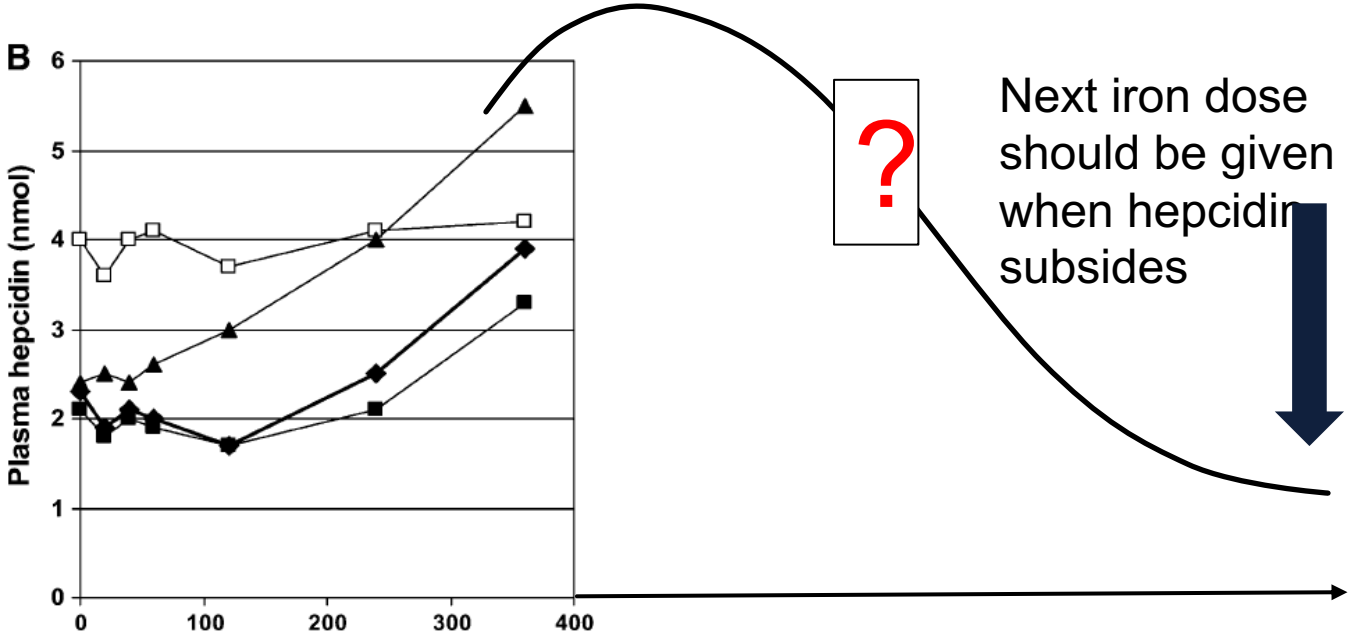
	Consecutive-day dosing for 14 days	Alternate-day dosing for 28 days	p value
Fractional iron absorption, %			
Week 1, first seven doses	16·1 (8·9, 28·9)	21·3 (13·2, 34·3)	0·13
Week 2, second seven doses	16·6 (9·4, 29·6)	22·3 (13·9, 35·8)	0·11
All 14 doses	16·3 (9·3, 28·8)	21·8 (13·7, 34·6)	0·0013
Total 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

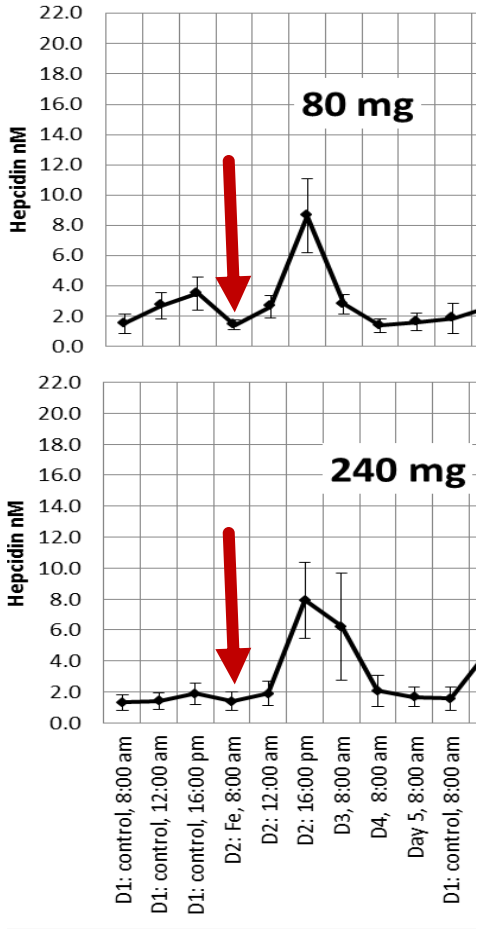
Data are geometric means (–SD, +SD). Analysed with mixed-effect models with group as fixed factor and participant as random factor (fixed-effect estimation obtained with bootstrapping).

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.

High plasma hepcidin sharply reduces iron absorption

A single oral dose of Fe induces a hepcidin rise





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

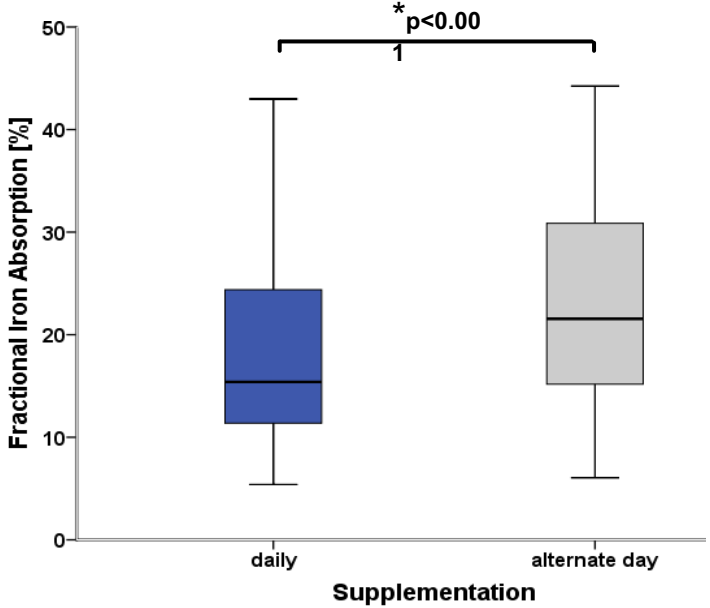
Moretti et al. Blood 2015

Alternate day dosing of 60 mg iron increases fractional and total absorption by 30%

14 doses of 60 mg given on alternate days deliver 20 mg more absorbed iron than when given daily

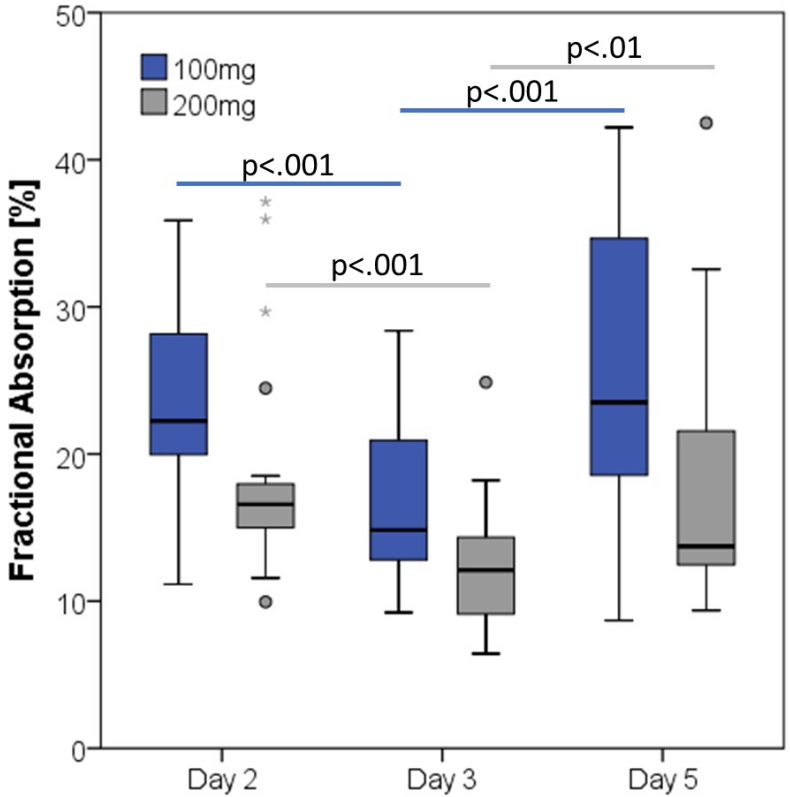
Total iron absorbed (mg)	
daily	67 (39, 114)
alternate	88 (56, 138)

GI side effects 33% less frequent in the alternate day group



Stoffel et al. Lancet Hematology 2018

In women with IDA, alternate day dosing of 100 or 200 mg increases absorption by 35-47%



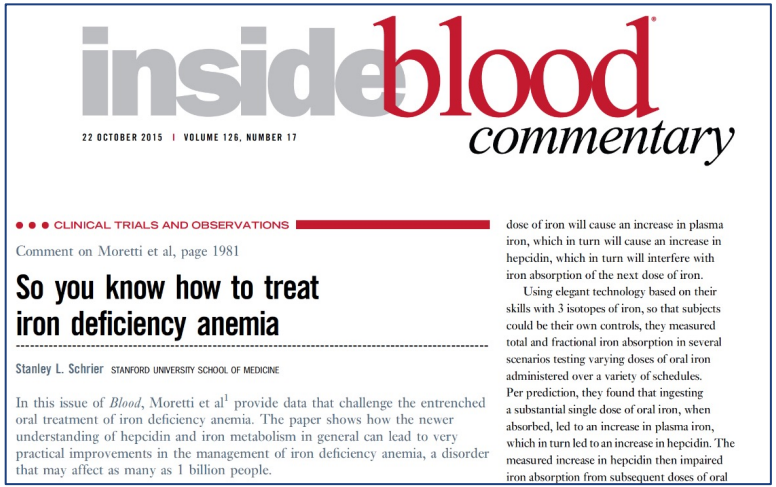
Doses of 100mg ≈50% less GI side effects compared to 200mg

Stoffel et al. Hematologica 2020

Conclusions

- Large oral doses of Fe trigger an acute hepcidin surge that reduces iron absorption 24 hr later, but not 48 hr later

- Alternate day dosing increases iron absorption by 30-50% and may reduce side effects in women with ID (60 mg) and IDA (100 and 200 mg)



inside blood commentary

22 OCTOBER 2015 | VOLUME 126, NUMBER 17

CLINICAL TRIALS AND OBSERVATIONS

Comment on Moretti et al, page 1981

So you know how to treat iron deficiency anemia

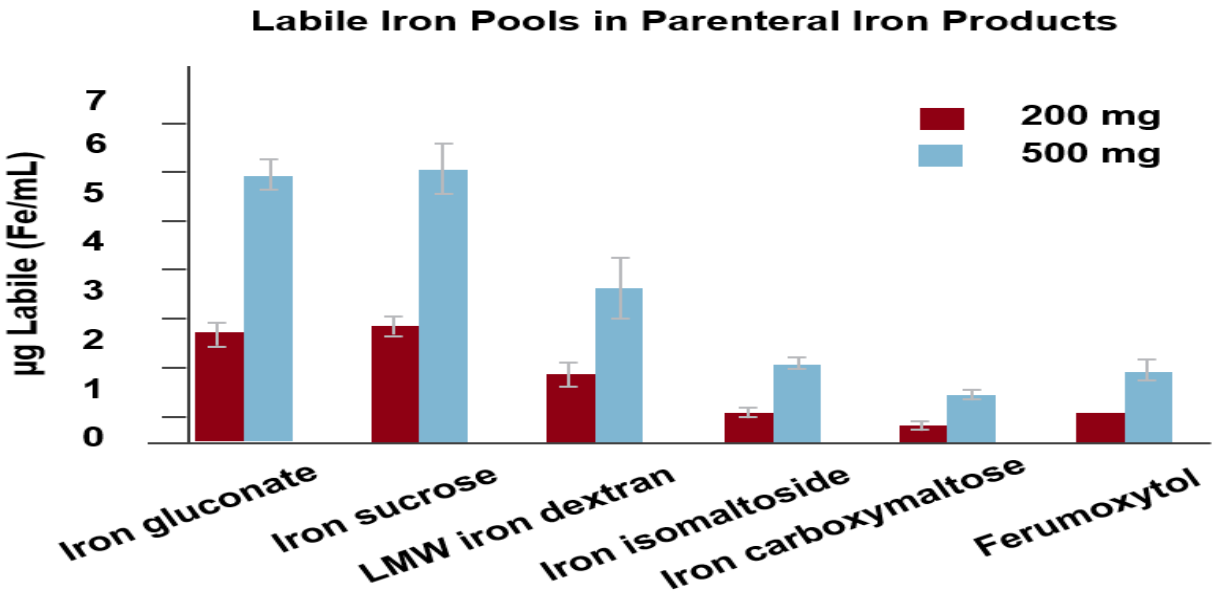
Stanley L. Schrier STANFORD UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Moretti et al[1] provide data that challenge the entrenched oral treatment of iron deficiency anemia. The paper shows how the newer understanding of hepcidin and iron metabolism in general can lead to very practical improvements in the management of iron deficiency anemia, a disorder that may affect as many as 1 billion people.

dose of iron will cause an increase in plasma iron, which in turn will cause an increase in hepcidin, which in turn will interfere with iron absorption of the next dose of iron.

Using elegant technology based on their skills with 3 isotopes of iron, so that subjects could be their own controls, they measured total and fractional iron absorption in several scenarios testing varying doses of oral iron administered over a variety of schedules. Per prediction, they found that ingesting a substantial single dose of oral iron, when absorbed, led to an increase in plasma iron, which in turn led to an increase in hepcidin. The measured increase in hepcidin then impaired iron absorption from subsequent doses of oral

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.

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

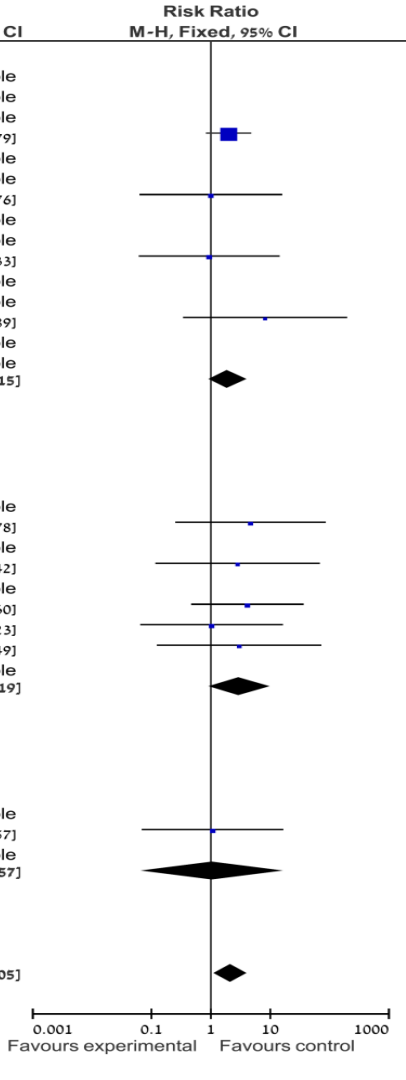
IV Iron Safety

- 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

Forest Plot: Composite Safety Meta-analysis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Pregnancy						
Al 2005	0	45	0	45		Not estimable
Al Momen 1996	0	52	0	59		Not estimable
Bayoumeu 2002	0	24	0	23		Not estimable
Bencaiova 2009	14	130	7	130	50.3%	2.00 [0.83, 4.79]
Dawson 1965	0	153	0	47		Not estimable
Dhanani 2012	0	29	0	23		Not estimable
Khalafallah 2010	1	98	1	98	7.2%	1.00 [0.06, 15.76]
Kochhar 2012	0	50	0	50		Not estimable
Neeru 2012	0	45	0	44		Not estimable
Oluboyede 1980	1	32	1	30	7.4%	0.94 [0.06, 14.33]
Shafi 2013	0	100	0	100		Not estimable
Singh 1998	0	50	0	50		Not estimable
Sood 1979	1	32	0	89	1.9%	8.18 [0.34, 195.89]
Stein 1991	0	60	0	30		Not estimable
Wali 2002	0	35	0	25		Not estimable
Subtotal (95% CI)		**935**		**843**	**66.9%**	**1.95 [0.92, 4.15]**
Total events	17		9			
Heterogeneity: Chi² = 1.29, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.74 (P = 0.08)						
1.6.2 Peripartum						
Bhandal 2006	0	22	0	21		Not estimable
Breymann 2008	4	227	0	117	4.7%	4.66 [0.25, 85.78]
Daniilidis 2011	0	109	0	26		Not estimable
Froessler 2013	1	100	0	94	3.7%	2.82 [0.12, 68.42]
Giannoulis 2009	0	52	0	20		Not estimable
Seid 2008	4	142	1	147	7.1%	4.14 [0.47, 36.60]
Van Wyck 2007	1	174	1	178	7.1%	1.02 [0.06, 16.23]
Verma 2011	1	75	0	75	3.6%	3.00 [0.12, 72.49]
Westad 2008	0	58	0	70		Not estimable
Subtotal (95% CI)		**959**		**748**	**26.2%**	**3.05 [0.91, 10.19]**
Total events	11		2			
Heterogeneity: Chi² = 0.76, df = 4 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.81 (P = 0.07)						
1.6.3 Uterine bleeding / Other						
Kim 2009	0	30	0	30		Not estimable
Krayenbuehl 2011	1	43	1	46	6.9%	1.07 [0.07, 16.57]
Van Wyck 2009	0	228	0	225		Not estimable
Subtotal (95% CI)		**301**		**301**	**6.9%**	**1.07 [0.07, 16.57]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**2195**		**1892**	**100.0%**	**2.18 [1.17, 4.05]**
Total events	29		12			
Heterogeneity: Chi² = 2.58, df = 9 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.46 (P = 0.01)						
Test for subgroup differences: Chi² = 0.63, df = 2 (P = 0.73), I² = 0%						



Randomised controlled trials investigating hypersensitivity reactions as a prespecified study endpoint

Highest-quality evidence
RCTs are the 'gold standard'

- The highest-quality evidence for clinical outcome can be obtained from RCTs[1] – the 'gold standard'
- The newest and highest-level evidence comes from a number of robust RCTs that were designed and powered to evaluate serious or moderate-to-severe HSRs as a pre-specified primary or secondary endpoint[2]
- Iron sucrose (IS) has consistently shown a low risk of hypersensitivity in clinical trials and, from a regulatory authority perspective, is considered the benchmark for comparison when evaluating HSRs

HSR=hypersensitivity reaction; IS=iron sucrose; RCT=randomised controlled trial

1. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence; 2. Deloughery et al. In preparation

FERWON-NEPHRO and FERWON-IDA trials
Powered to assess risk of HSRs

The FERWON trial program consists of two trials:

- FERWON-IDA included patients with iron deficiency anaemia (IDA) of mixed aetiologies[1]
- FERWON-NEPHRO included patients with non-dialysis-dependent CKD (NDD-CKD)[2]

- The FERWON program was powered on the risk of serious or severe hypersensitivity reactions (HSRs) comparing iron isomaltoside 1000 (IIM) against the widely used intravenous (IV) iron formulation, iron sucrose (IS)[1,2]

CKD=chronic kidney disease; HSR=hypersensitivity reaction; IDA=iron deficiency anaemia; IIM=iron isomaltoside 1000; IS=iron sucrose; IV=intravenous; NDD=non-dialysis-dependent

1. Auerbach et al. Am J Hematol 2019 [Epub]; 2. Bhandari et al. Poster at ERA-EDTA 2019

Methods – endpoints

Co-primary endpoints:[1,2]

- Adjudicated serious or severe HSRs[a] starting on or after the first dose of treatment
- Change in haemoglobin (Hb) from baseline to Week 8 (data not presented here)

- Adjudication of hypersensitivity and composite cardiovascular AEs was performed in a blinded fashion by an independent Clinical Endpoint Adjudication Committee[1,2]

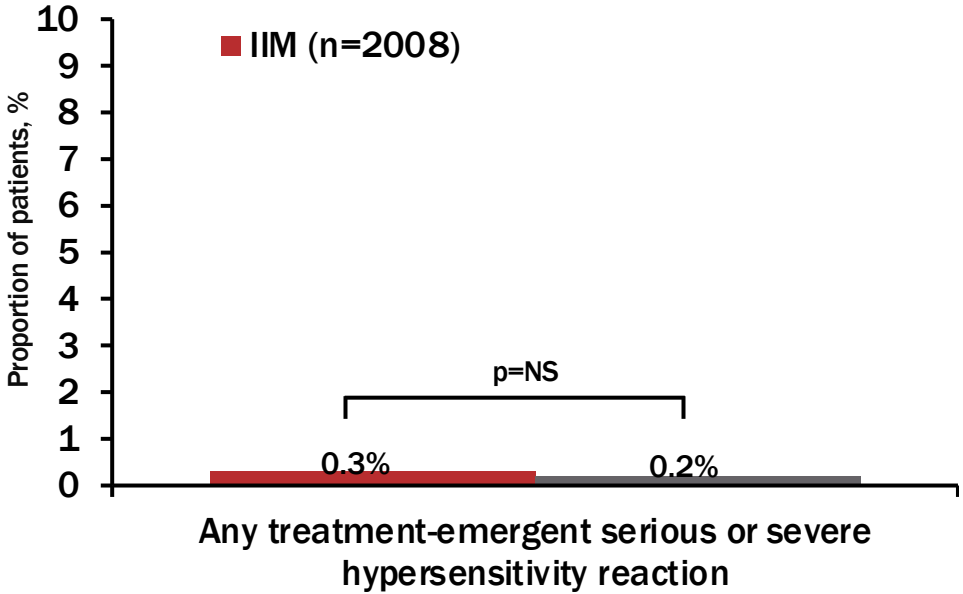
[a]The hypersensitivity terms were defined by a standardised set of Medical Dictionary for Regulatory Activities (MedDRA) terms based on discussions with the US Food and Drug Administration.[1,2] Seriousness was defined according to the conventional criteria for serious adverse events, and severity was defined as an adverse event that produces significant impairment of functioning or incapacitation and is a hazard to the subject[2]

AE=adverse event; Hb=haemoglobin; HSR=hypersensitivity reaction

1. Auerbach et al. Am J Hematol 2019 [Epub]; 2. Bhandari et al. Poster at ERA-EDTA 2019

Incidence of adjudicated and confirmed serious or severe hypersensitivity reactions

Hypersensitivity reactions



There was no significant difference in the frequency of patients with serious or severe HSRs between the IIM and IS treatment groups

Safety analysis set
HSR=hypersensitivity reaction; IIM=iron isomaltoside; IS=iron sucrose; NS=not significant
Bhandari et al. Poster at ERA-EDTA 2019

FIRM study
Powered to assess risk of HSRs

- Randomised, multi-center, double-blind trial of ferumoxytol (FER) 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;93(5):683–690

Methods – design

Study sites (129) in the US, Latvia, Lithuania, Canada, Hungary, and Poland

- Adults with IDA of any aetiology, excluding dialysis-dependent CKD:
  - Gastrointestinal disorders (29%)
  - Chronic kidney disease (27%)
  - Abnormal uterine bleeding (25%)
  - Other (19%)
- 1997 adults (safety population) were randomised 1:1 to:
  - FER 2 x 510 mg (1020 mg)
  - FCM 2 x 750 mg (1500 mg)
  - First IV dose on Day 1, second dose 7 to 8 days later

CKD=chronic kidney disease; FCM=ferric carboxymaltose; FER=ferumoxytol; IDA=iron deficiency anaemia; IV=intravenous

Adkinson et al. Am J Hematol 2018;93(5):683–690

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

CEC=Clinical Events Committee; HSR=hypersensitivity reaction

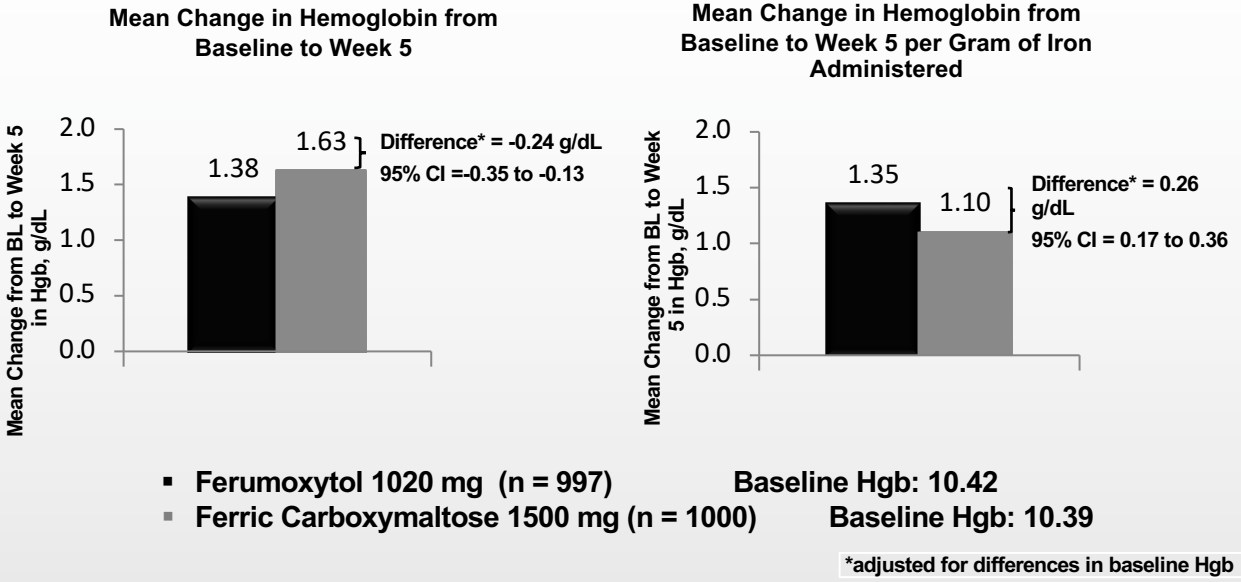
Adkinson et al. Am J Hematol 2018;93(5):683–690

Primary endpoint composite and components

	Treatment group, n (%)		Treatment difference (95% CI)	Relative risk (95% CI)	Non-inferiority p-value
	FER (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)			

aFrom 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; FER=ferumoxytol
Adkinson et al. Am J Hematol 2018;93(5):683–690

Ferumoxytol IDA Trial 3 (FIRM): Change in Hemoglobin from Baseline to Week 5



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

Feraheme® [prescribing information]. Waltham, MA: AMAG Pharmaceuticals, Inc; February 2018;
Adkinson et al. *Am J Hematol* 2018.

PHOSPHARE-IDA04/IDA05 trials
Assessed risk of HSRs

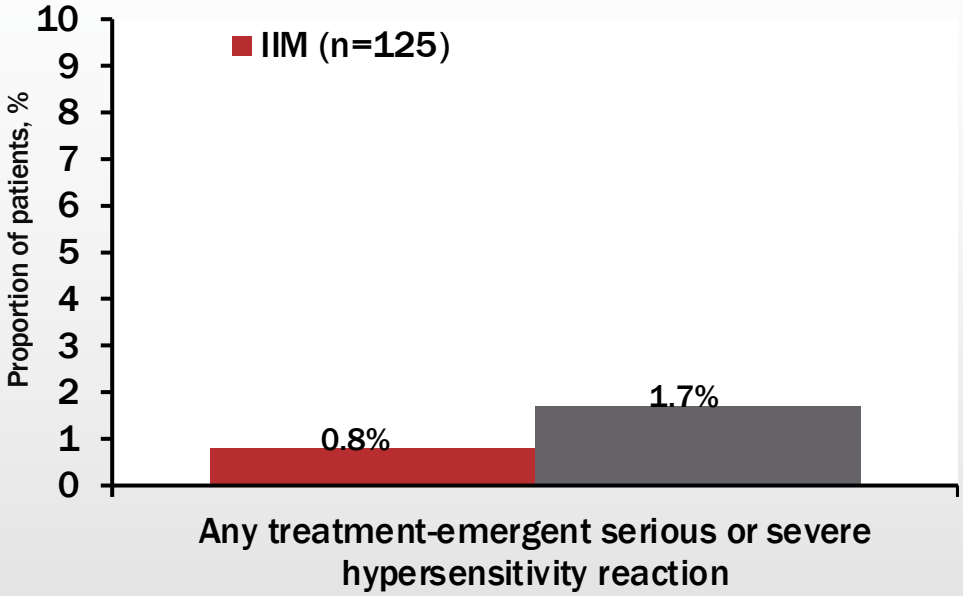
- Two, identically-designed, open-label, randomised clinical trials
- Adults (n=245) with IDA were randomised 1:1 to receive:
  - IIM, single infusion of 1000 mg on Day 0 or
  - FCM, two infusions of 750 mg administered 1 week apart (first infusion on Day 0 and second infusion on Day 7)
- Safety endpoints included the number of patients who experienced serious or severe hypersensitivity reactions

FCM=ferric carboxymaltose; HSR=hypersensitivity reaction; IDA=iron deficiency anaemia; IIM=iron isomaltoside 1000

Wolf et al. J Endocr Soc 2019;3(Suppl 1):OR13-3

Rates of HSRs were low in both groups

Hypersensitivity reactions



There were three serious or severe HSRs:

- One (swollen eyelid unilaterally) in the IIM group (0.8%)
- Two (swelling, and dyspnoea) in the FCM group (1.7%)

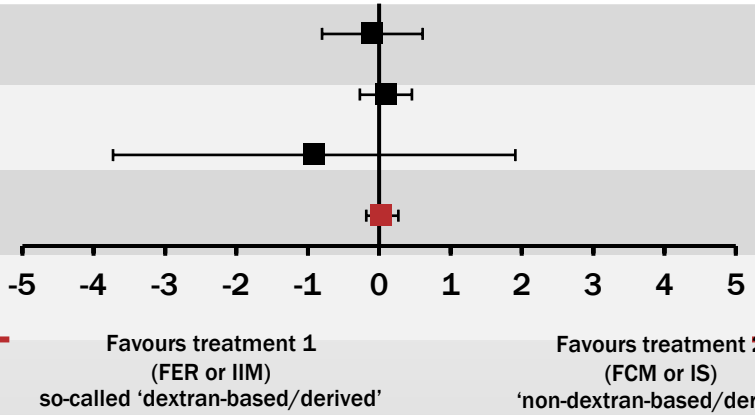
FCM=ferric carboxymaltose; HSR=hypersensitivity reaction; IIM=iron isomaltoside 1000

Zoller et al. Poster at NATA 2019

No clinical meaning or relevance of so-called dextran-derived vs non-dextran derived categorisation of IV irons

An insidious drive to categorize IV iron products as either ‘dextran-based/derived’ or ‘non-dextran-based/derived’ has led to the misbelief that all products with dextran-derived carbohydrate components are associated with a higher risk of severe HSRs[1]

Study (treatment 1:treatment 2)	Incidence of HSRs, n/N (%) Treatment 1	Treatment 2	Risk difference (unadjusted 95% CI)
Adkinson (FER:FCM)	6/997 (0.60%)	7/1000 (0.70%)	-0.10 (-0.80, 0.61)
FERWON (IIM:IS)	6/2008 (0.30%)	2/1000 (0.20%)	0.10 (-0.27, 0.46)
PHOSPHARE (IIM:FCM)	1/125 (0.80%)	2/117 (1.71%)	-0.91 (-3.73, 1.91)
Pooled (FER/IIM:FCM/IS)	13/3130 (0.42%)	11/2117 (0.52%)	0.04 (-0.18, 0.27)



CI=confidence interval; FCM=ferric carboxymaltose; FER=ferumoxytol; HSR=hypersensitivity reaction; IIM=iron isomaltoside 1000; IS=iron sucrose

Deloughery et al. In preparation

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.

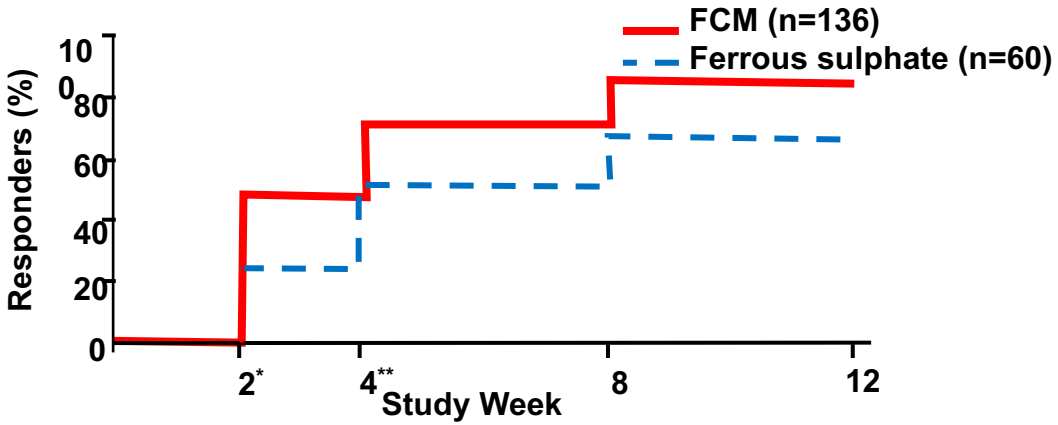
Oral versus intravenous iron distinctly alters gut microbiota in IBD

- 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)



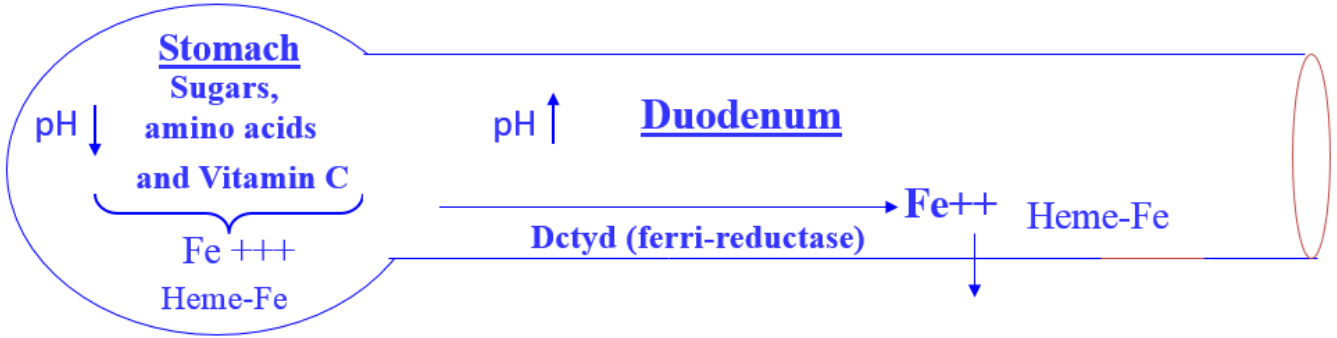
DOSING:

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.

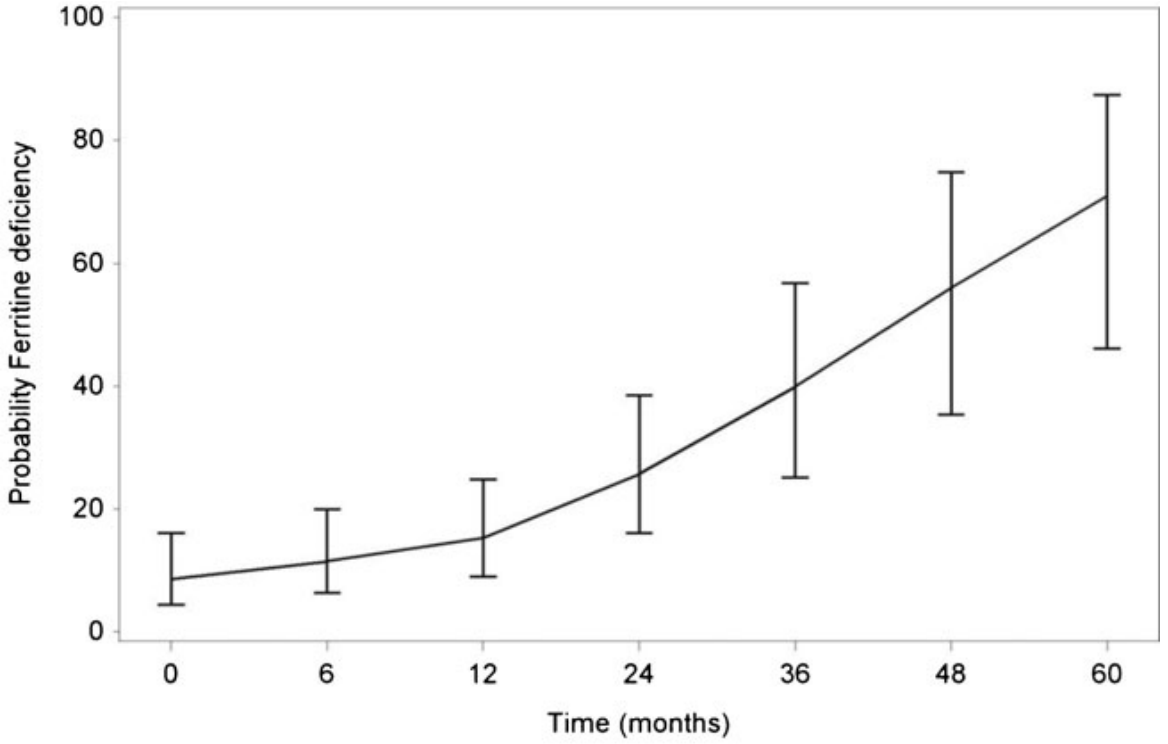
Treatment comparison log-rank test 0.009. **P*=0.0051; ***P*=0.0346.
Kulnigg S, et al. *Am J Gastroenterol*. 2008;103:1182-1192

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

Better Response with IV iron in Bariatric Surgery

Study number (n=240)	Baseline hemoglobin value		Highest hemoglobin value		Change to highest hemoglobin value	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Study 2 (65)						
Ferric carboxymaltose (29)	9.6 (1.08)	9.9	12.8 (0.80)	12.9	3.2 (1.32)	3.4
Iron sucrose or ferric gluconate (13)	9.5 (1.20)	10.0	11.9 (1.18)	12.1	2.4 (0.84)*	2.2
Oral iron (17)	9.9 (0.95)	10.4	11.6 (1.49)	11.9	1.7 (1.11)*	1.4
Other treatment (6)	9.4 (1.09)	9.5	11.1 (1.04)	11.0	1.7 (0.43)*	1.7
Study 3 (31)						
Ferric carboxymaltose (16)	9.6 (1.25)	10.0	12.5 (1.15)	12.7	2.9 (1.82)	2.5
Iron dextran (15)	9.1 (1.67)	9.7	11.9 (0.89)	12.0	2.8 (1.62) NS	3.2
Study 4 (50)						
Ferric carboxymaltose (22)	10.3 (0.67)	10.4	11.5 (1.1)	11.3	1.2 (0.88)	1.1
Iron sucrose (28)	10.3 (0.64)	10.3	11.1 (0.81)	11.2	0.84 (0.72) NS	1.0
Study 5 (94)						
Ferric carboxymaltose (39)	9.2 (1.1)	9.1	12.4 (1.1)	12.5	3.2 (1.38)	3.2
Oral iron (11)	10.[illegible] (1.1)	10.3	10.8 (1.6)	10.7	0.61 (0.74)*	0.4
IV SMC (44)	9.3 (1.3)	9.8	11.4 (1.1)	11.5	2.08 (1.14)*	1.8

NS nonsignificant versus FCM

*p<0.05 versus FCM

Malone et al, *Ann Pharmacother* 2008;42:1851-1858

Response to FDI and IS in Bariatric Patients

Table 3 Frequency of responders and participants achieving target iron parameters

	FDI n/N (%)	IS n/N (%)	P-value[a]
Participants with Hb level increase ≥ 2 g/dL from baseline			
Week 1	5/91 (5.5)	0/62 (0.0)	0.0810
Week 2	33/91 (36.3)	4/61 (6.6)	< 0.0001
Week 4	63/91 (69.2)	37/61 (60.7)	0.2989
Participants with *s*-ferritin ≥ 100 ng/mL and TSAT of 20–50%			
Week 1	56/88 (63.6)	3/63 (4.8)	< 0.0001
Week 2	42/91 (46.2)	5/59 (8.5)	< 0.0001
Week 4	26/90 (28.9)	14/60 (23.3)	0.5722

Data are presented for the FAS

[a]FDI versus IS using a Fisher's exact test

FAS, full analysis set; FDI, ferric derisomaltose/iron isomaltoside 1000; Hb, hemoglobin; IS, iron sucrose; n, number of responders; N, number of patients; *s*-ferritin, serum ferritin; TSAT, transferrin saturation

Auerbach et al, Obesity Surgery, 2022

Change in Hemoglobin and Iron Parameters after Bariatric Surgery

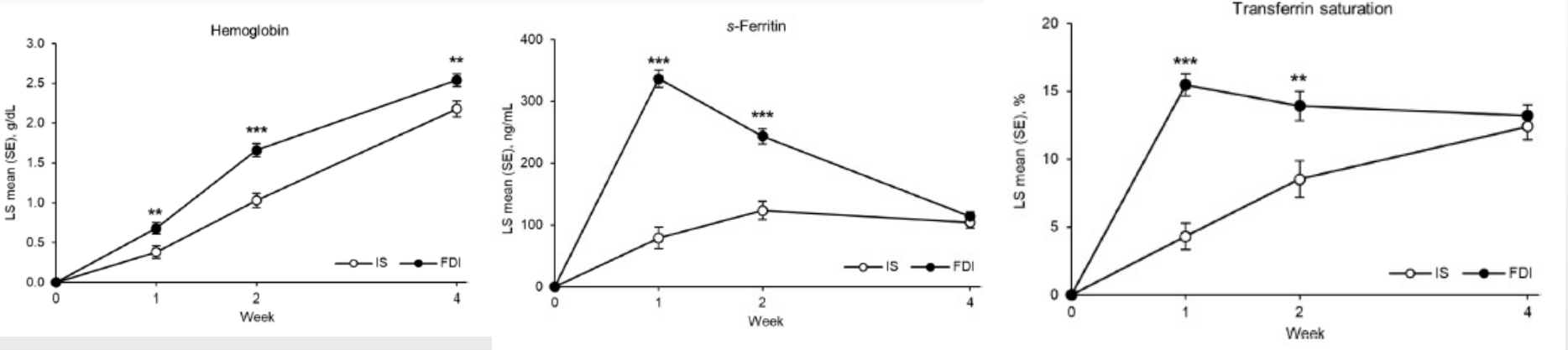


Fig. 1 LS mean change in hematological parameters from baseline over 4 weeks. **p<0.01, ***p<0.001 versus IS; estimates from mixed model for repeated measures with study, treatment and day as factors, treatment*day and baseline*day interactions, and baseline value as covariate. Data are presented for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

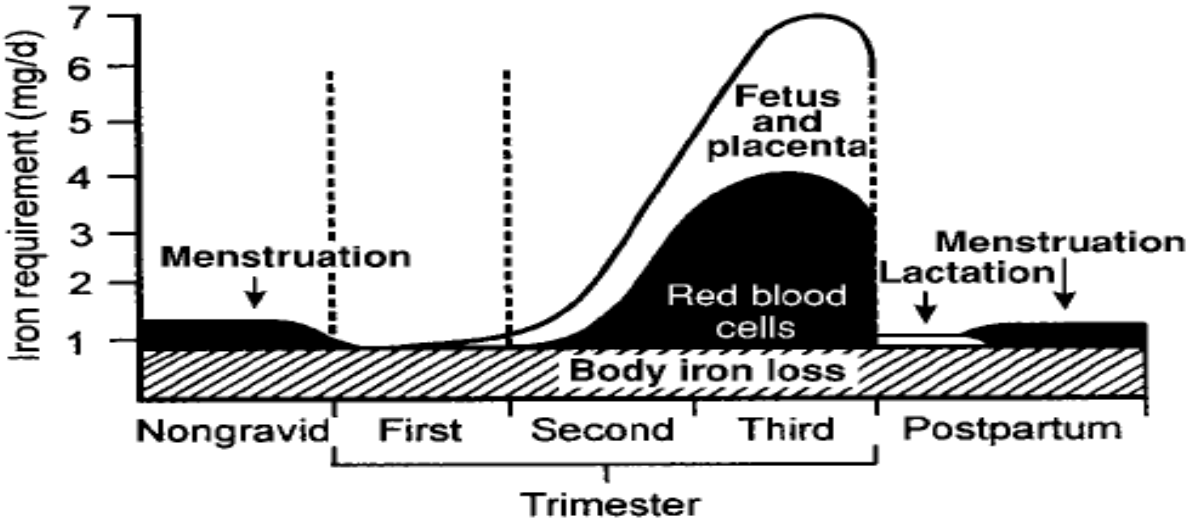
Auerbach et al, Obesity Surgery, 2022

Guidelines Differ

- USPSTF: “There is insufficient evidence that routine screening and supplementation for iron deficiency anemia improves maternal or infant clinical health outcomes”
- 2021 ACOG Practice Bulletin: “Intravenous iron is recommended who cannot tolerate or will not take modest doses of oral iron”. No recommendation for routine screening or treatment of non-anemic iron deficiency. PO still recommended as frontline therapy in 3rd trimester.
- 2019 UK guidelines: “Parenteral iron should be considered from the 2nd trimester onwards and during the postpartum period for women with confirmed ID who fail to respond to, or are intolerant of, oral iron”. High risk presenting gravidas should be screened for iron deficiency
- Blood 2017 Achebe and Gafter-Gvili: IV iron for any oral intolerant 2nd or 3rd trimester patient, for 2nd trimester gravidas with [Hb]<10.5 g/dl and all in the 3rd with ID
- No guidelines for non-anemic ID pregnant women

Pavord et al, Br J Haem in press, Achebe and Gafter Gvili, Blood 2017, ACOG Practice Bulletin, 2008, Cantor et al, AIM 2015

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]

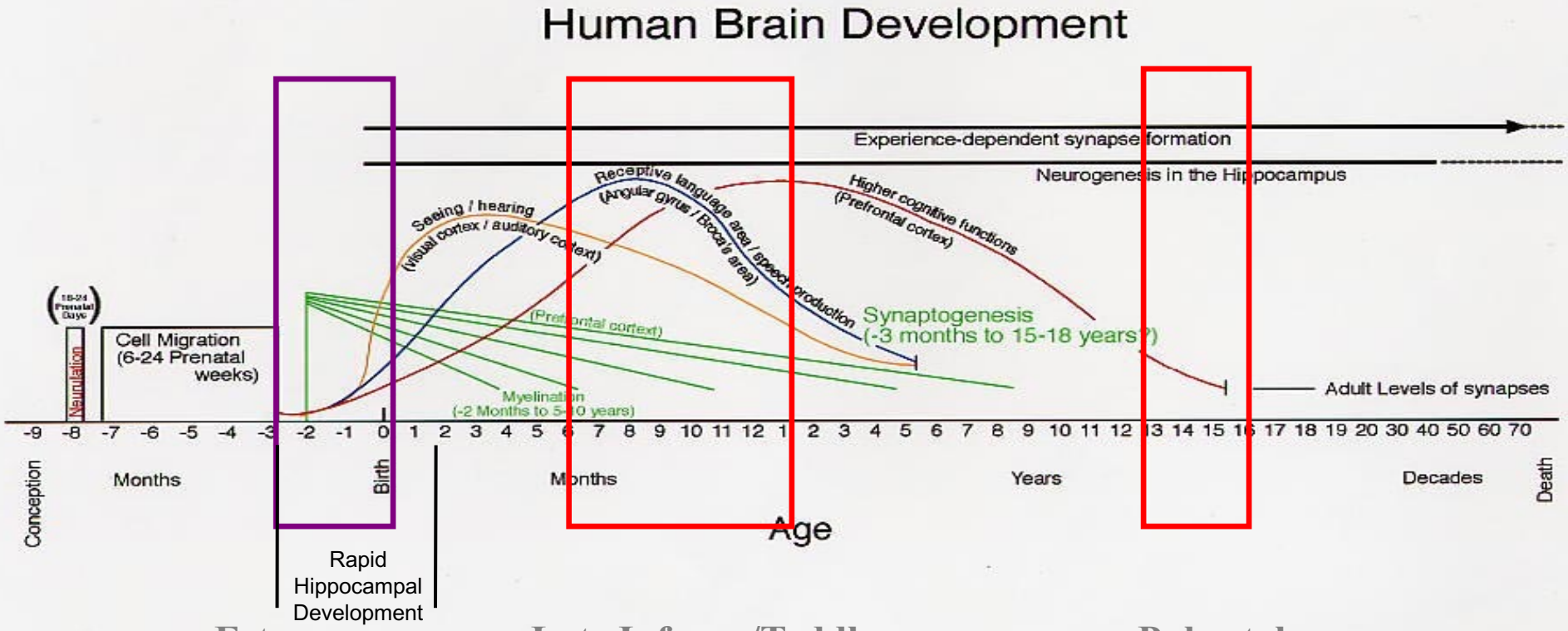
Iron deficiency anemia (IDA) in pregnancy has been associated with increased risk of adverse perinatal outcomes, including preterm birth, low birth weight, and small-for-gestational age infants[5-7]

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)

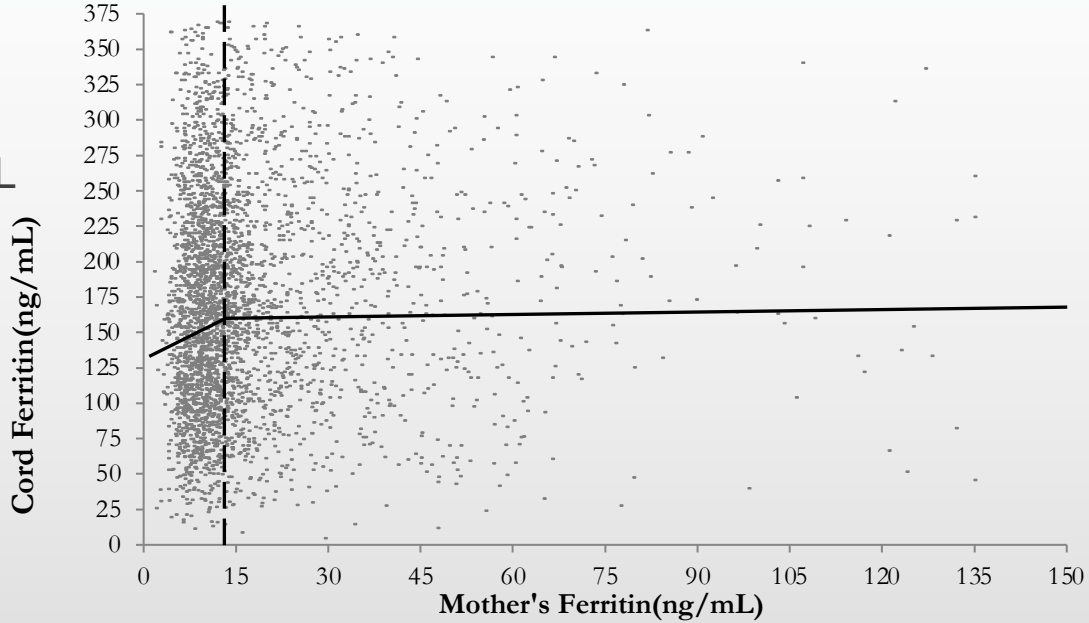
The Effect of Timing of ID on Brain Development



Georgieff, Pediatric Research, 2005

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

TSAT and ferritin levels by gravidity

	Gravidity=1 n=30	Gravidity=2 n=30	Gravidity=3 n=23	Gravidity=4+ n=19
TSAT, mean (SD)	25.4 (15.6)	27.4 (14.0)	25.0 (13.5)	32.7 (12.8)
TSAT, median (IQR)	20.5 (15, 33)	22.5 (16, 38)	21.0 (14, 35)	32 (23, 45)
Ferritin, mean (SD)	77.1 (56.1)	69.4 (37.4)	61.6 (43.1)	49.1 (22.9)
Ferritin, median (IQR)	68 (41, 94)	66 (41, 90)	40 (33, 81)	37 (32, 66)
TSAT <19, n(%)	13 (43)	12 (40)	9 (39)	4 (21)
Ferritin <20, n(%)	4 (13)	0 (0)	1 (4)	0 (0)
Ferritin <25, n(%)	4 (13)	1 (3)	1 (4)	0 (0)
Ferritin <30, n(%)	6 (20)	3 (10)	3 (13)	2 (10)

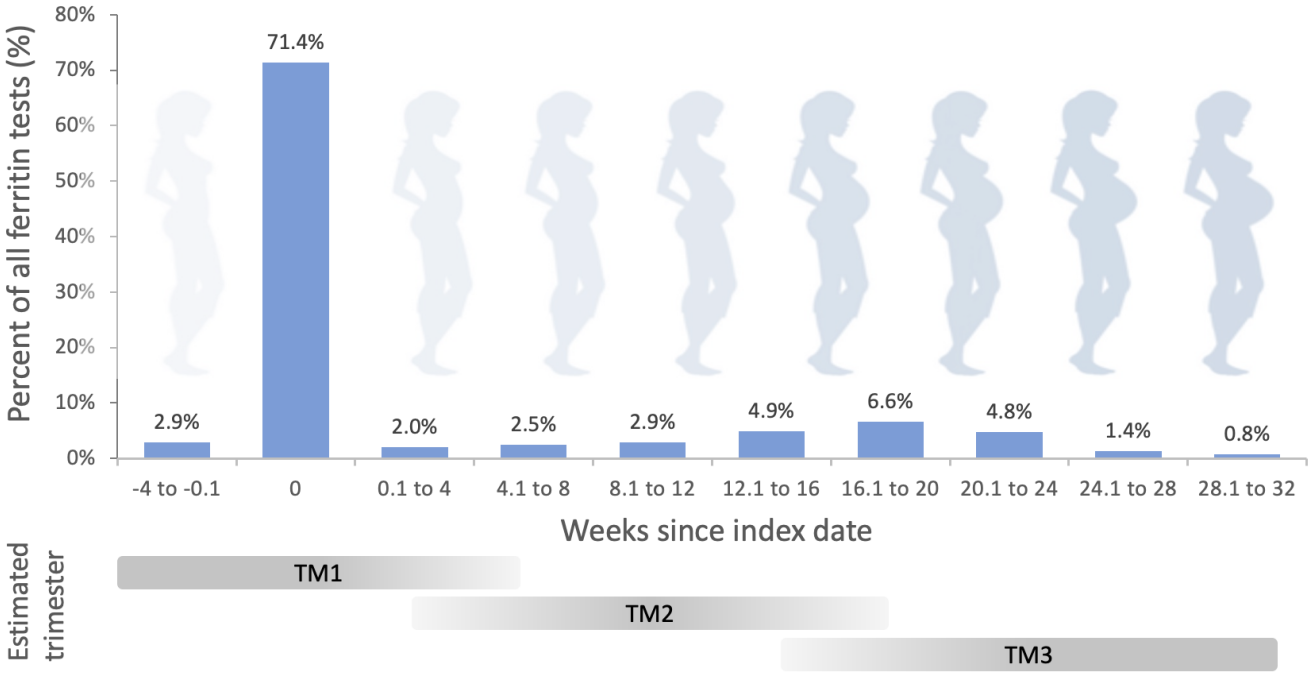
Table 2.

Auerbach et al, J Mat Fet Med, 2019

Results: Prevalence of ID

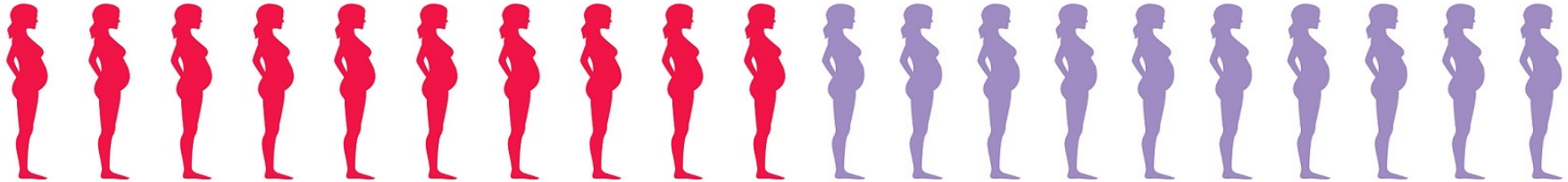
Iron Status (ferritin in µg/L)	Percent of women (n=25,880)
Ever normal (45-150)	45.6%
Ever iron insufficient (30-44.9)	25.2%
Ever iron deficient (<30)	52.8%
Ever severely iron deficiency (<15)	23.8%
Never iron deficient or insufficient (all ferritin levels 45-150)	30.2%

Results: When done, ID screening occurs early



Conclusions

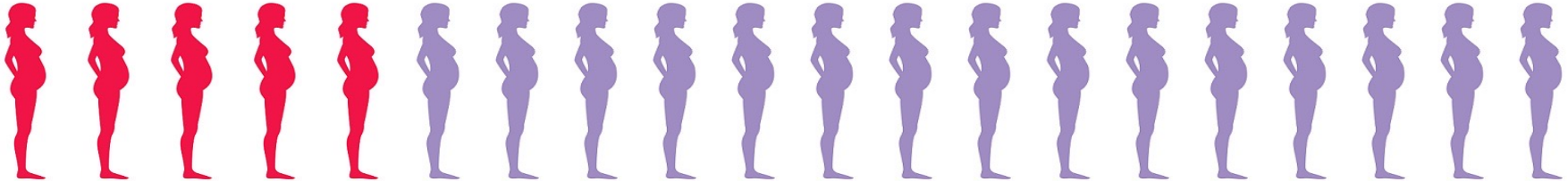
ID affects >50% of pregnancies in Ontario



Conclusions

ID affects >50% of pregnancies in Ontario

25% pregnancies are complicated by severe ID

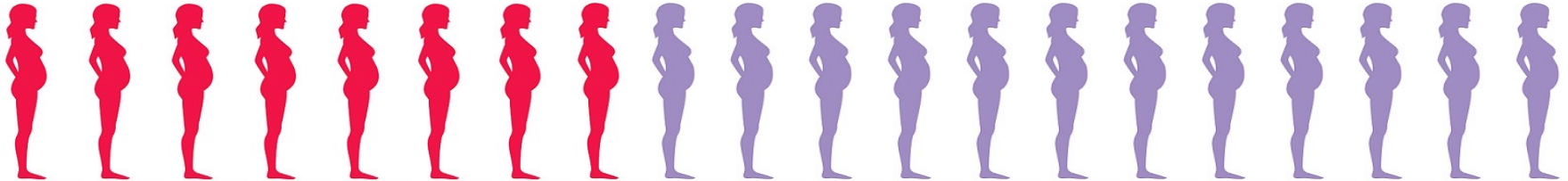


Conclusions

ID affects >50% of pregnancies in Ontario

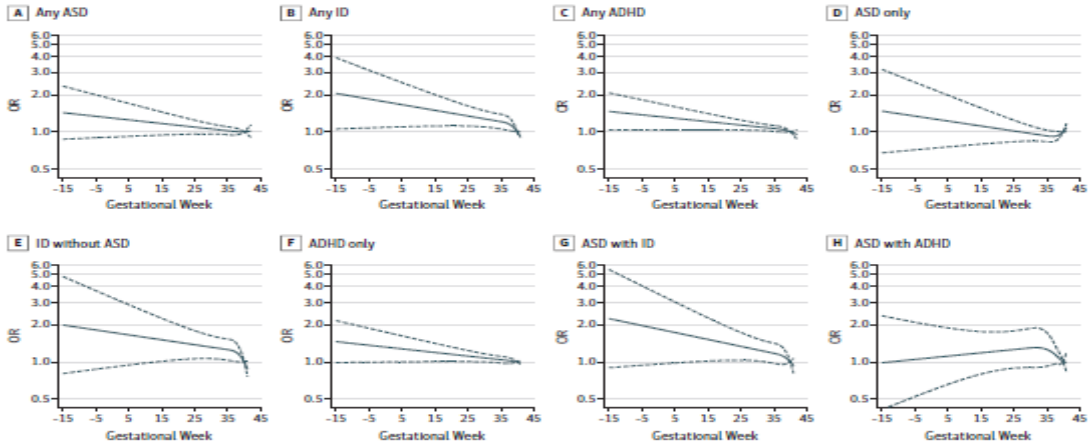
25% pregnancies are complicated by severe ID

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

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]

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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