

Iron management in Maternity Patients



Dr Natalie Cromer

Haematologist and Obstetric Physician

September 2022

First,
let's go through
interpretation of iron
studies in general

IRON STUDIES

Request Number		15629827
Date Collected		7 Oct 21
Time Collected		09:43
Specimen Type:	Serum	
Iron (10-30)	umol/L	
T'ferrin(27-46)	umol/L	
T. Sat. (13-45)		
Ferritin(30-400)	ug/L	1865

IRON STUDIES

Request Number		25340670	15629827
Date Collected		22 Oct 20	7 Oct 21
Time Collected		10:20	09:43
Specimen Type:	Serum		
Iron (10-30)	umol/L	22	
T'ferrin(27-46)	umol/L	34	
T. Sat. (13-45)		33	
Ferritin(30-400)	ug/L	1729	1865

Iron Studies

Iron	H 31.1	umol/L	(5.0 - 30.0)
Transferrin	L 1.6	g/L	(2.0 - 3.2)
TIBC (Calculated)	L 39	umol/L	(46 - 70)
Saturation	H 80	%	(10 - 45)
Ferritin	H 443	ug/L	(30 - 300)
Comment on Lab ID 846493299			

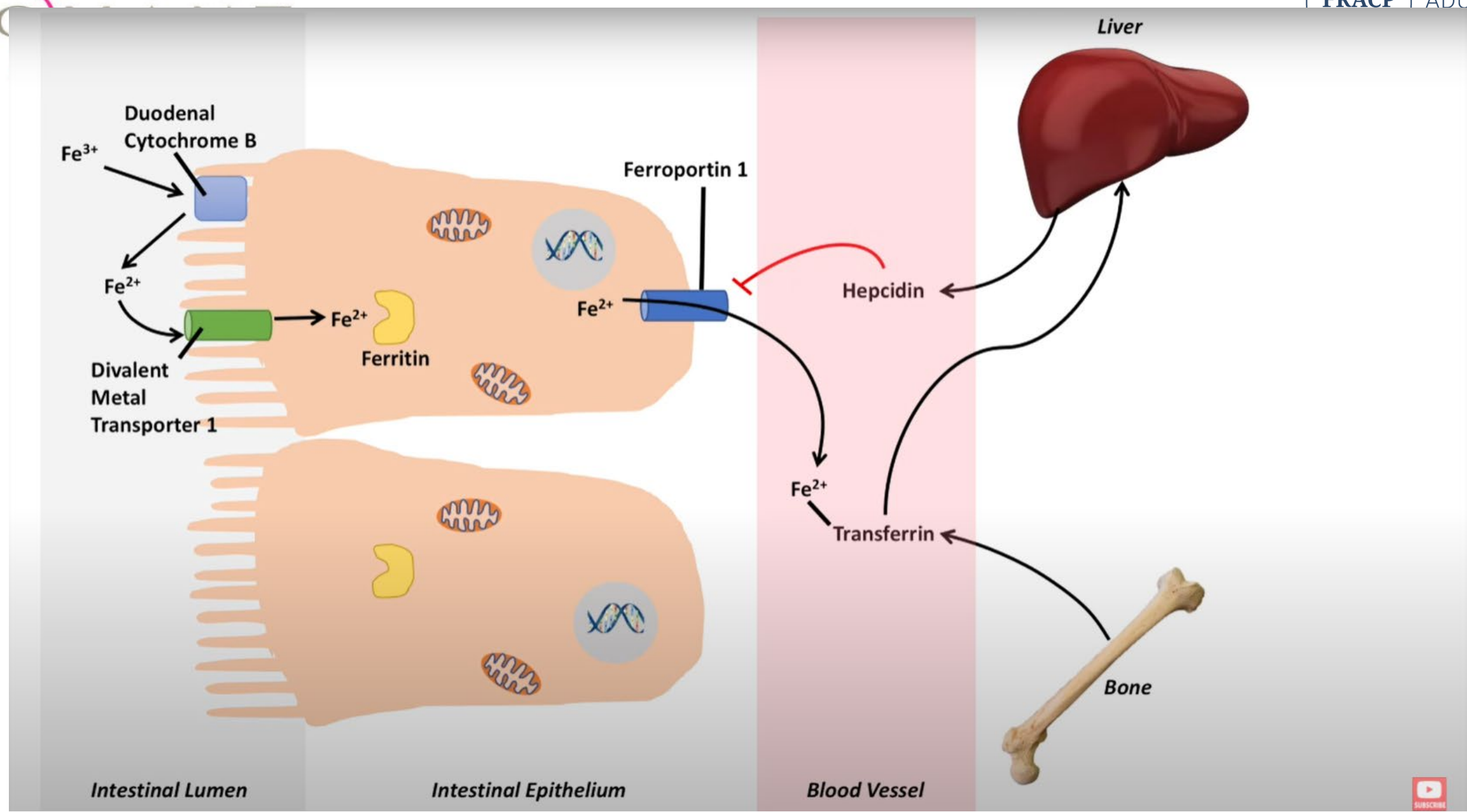
Iron Studies		
<input type="checkbox"/> Iron	8 umol/L	8 - 30
<input type="checkbox"/> Transferrin	2.6 g/L	1.8 - 3.5
<input type="checkbox"/> Ferritin	53 ug/L	30 - 150

Iron Studies		
<input type="checkbox"/> Iron	8 umol/L	8 - 30
<input type="checkbox"/> Transferrin	2.6 g/L	1.8 - 3.5
<input type="checkbox"/> Ferritin	53 ug/L	30 - 150
<input type="checkbox"/> Transferrin Saturation (%)	12 % L	15 - 45

Iron Studies	
<input type="checkbox"/> Iron	11 umol/L
<input type="checkbox"/> Transferrin	3.7 g/L H
<input type="checkbox"/> Ferritin	15 ug/L L
<input type="checkbox"/> Transferrin Saturation (%)	11 % L

- How do we interpret iron studies??
- Ferritin is low = Iron deficiency
 - How to diagnose it
 - Why do we care
 - How to treat it
 - Oral and IV options
- Ferritin is high
 - Inflammation (hepatic)
 - True iron overload (HH)
 - How does this affect pregnancy?



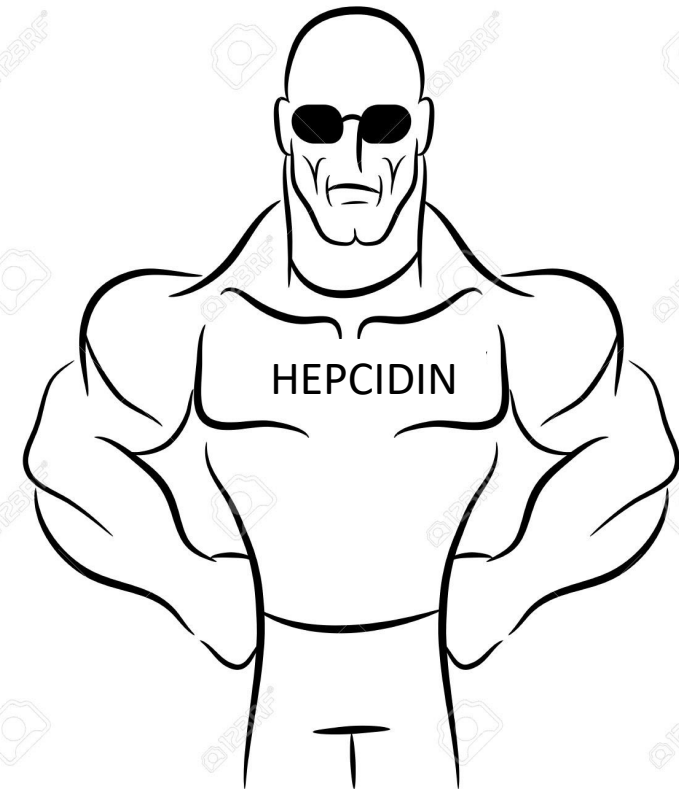


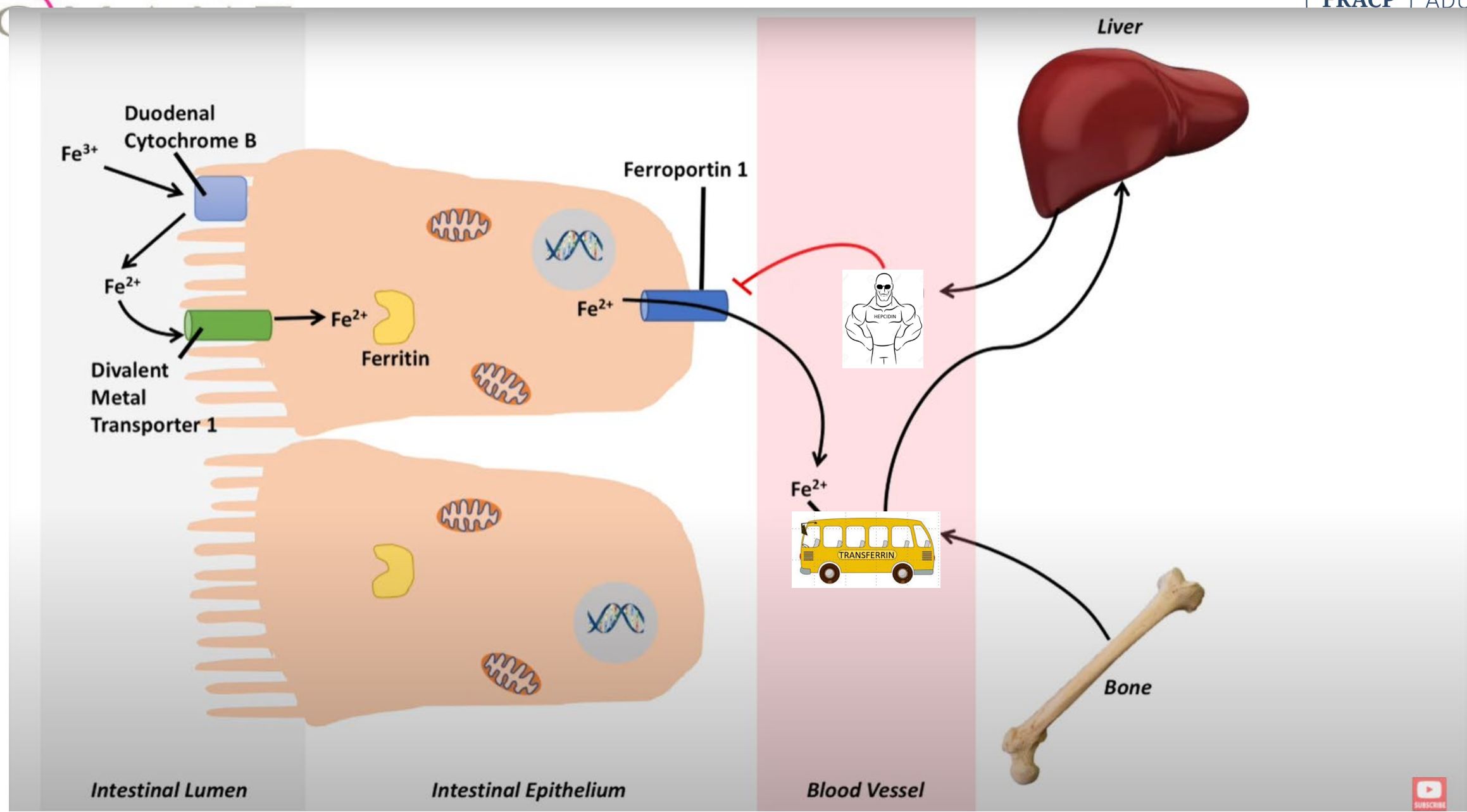
Two key players

- Transferrin
- Hepcidin



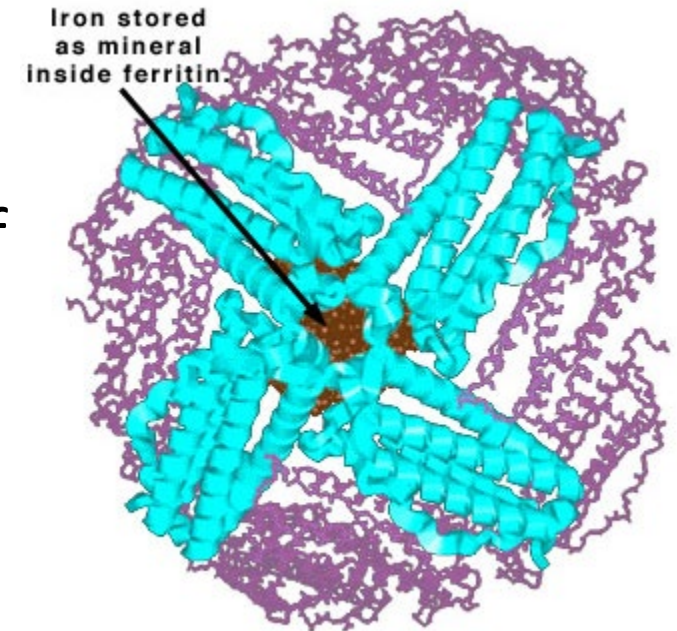
shutterstock.com · 567637843





Iron Studies	
<input type="checkbox"/> Iron	17 umol/L
<input type="checkbox"/> Transferrin	2.4 g/L
<input type="checkbox"/> Ferritin	94 ug/L
<input type="checkbox"/> Transferrin Saturation (%)	27 %

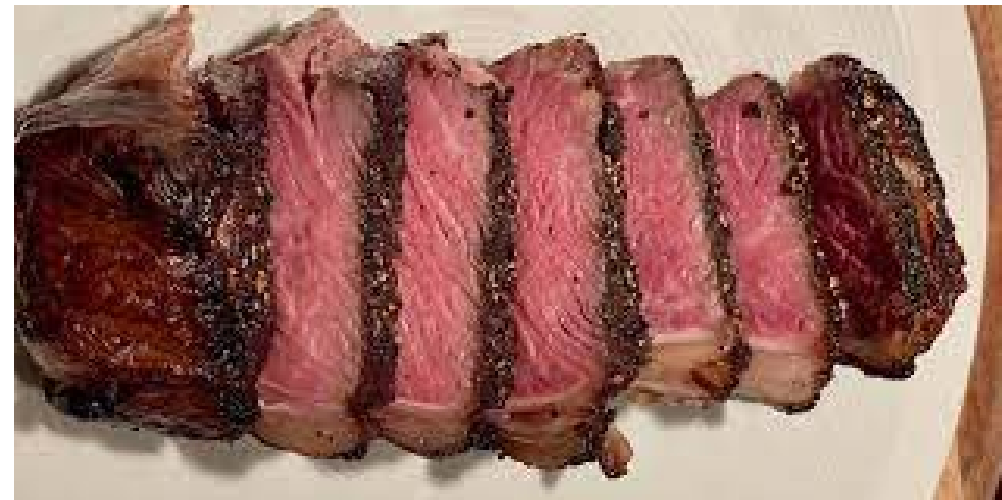
- “buffer”
- stores iron and releases it in a controlled fashion
- Is an *acute phase reactant*
- Spherical protein shell with a **variable** amount of iron as a core of ferric oxide-phosphate
 - Up to 20% iron when fully saturated



Serum iron

- Very dynamic
- Reflects recent dietary intake
- Used to calculate TSAT
- IGNORE

Iron Studies	
<input type="checkbox"/> Iron	17 umol/L
<input type="checkbox"/> Transferrin	2.4 g/L
<input type="checkbox"/> Ferritin	94 ug/L
<input type="checkbox"/> Transferrin Saturation (%)	27 %



Transferrin (or TIBC)

- Measures availability to transport iron (your buses)
- Transferrin is measured directly, TIBC is calculated – essentially gives you the same information
- ↑ in iron deficiency
- ↓ in inflammation (*negative acute phase reactant*)

Iron Studies			
Iron	H 31.1	umol/L	(5.0 - 30.0)
Transferrin	L 1.6	g/L	(2.0 - 3.2)
TIBC (Calculated)	L 39	umol/L	(46 - 70)
Saturation	H 80	%	(10 - 45)
Ferritin	H 443	ug/L	(30 - 300)
Comment on Lab ID 846493299			



Transferrin saturation (TSAT) - %

- Measures the ratio of iron to transferrin
- ie how full are your buses?
- Also reflected by recent intake
 - best interpreted fasting
 - But low is low



shutterstock.com - 567637843

Iron Studies	
<input type="checkbox"/> Iron	11 umol/L
<input type="checkbox"/> Transferrin	3.7 g/L H
<input type="checkbox"/> Ferritin	15 ug/L L
<input type="checkbox"/> Transferrin Saturation (%)	11 % L

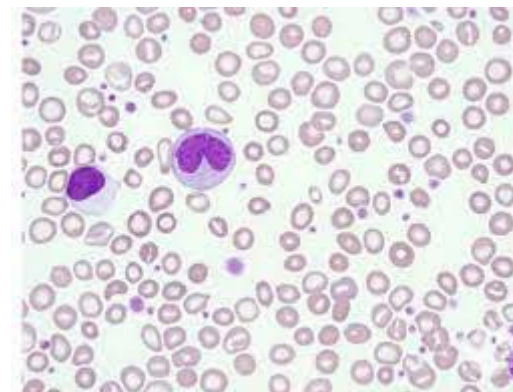
Hepcidin

- ↓ in response to iron deficiency
- ↓ in pregnancy
- ↑ following iron load
- ↑ in inflammation
 - a big contributor to anaemia of chronic disease / iron restricted erythropoiesis
- Not a diagnostic test ... but consider it as the underlying mechanism



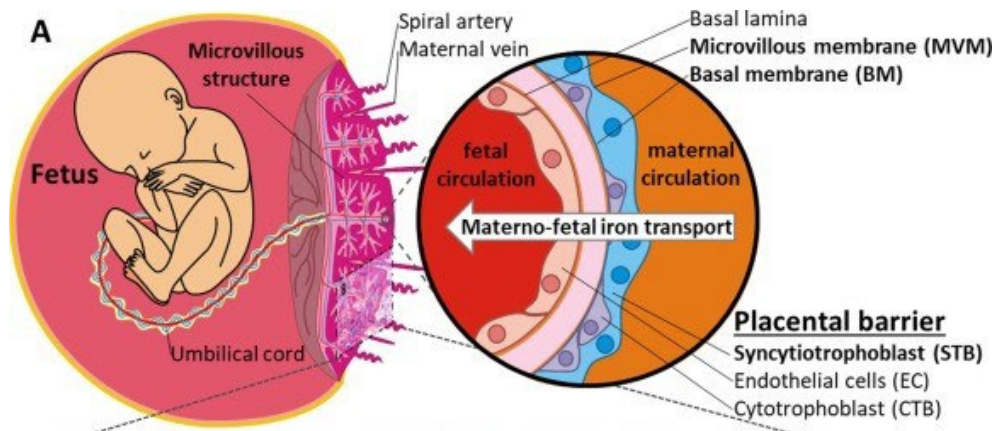
Iron deficiency

- Ferritin is low
 - OR
 - Ferritin is normal AND transferrin saturation is low = FUNCTIONAL iron deficiency (AKA iron restricted erythropoiesis)
 - Abnormal iron studies PRECEDE anaemia
-
- Severe iron deficiency:
 - Microcytosis, then anaemia



Obstetric iron requirements

- Increased maternal erythropoiesis and metabolic activity
- Placental development and metabolic activity
- Fetal erythropoiesis, development, metabolic activity and iron loading
- 1g iron throughout pregnancy (for those going in iron replete)



Diagnosis

- WHO states ferritin < 15 ug/L
 - Mean ferritin concentration was 15.1 ug/L when bone marrow iron was absent
 - Mean ferritin concentration was 70.4 ug/L when bone marrow iron was present
- RCPA recommends ferritin < 30 ug/L
 - Ferritin < 15 ug/L has a specificity of 99%, sensitivity only 75%
 - Ferritin < 30 ug/L has a specificity of 92%, sensitivity 92%
- We would recommend ferritin > 30 ug/L in pregnancy

Why is iron deficiency important in pregnancy?

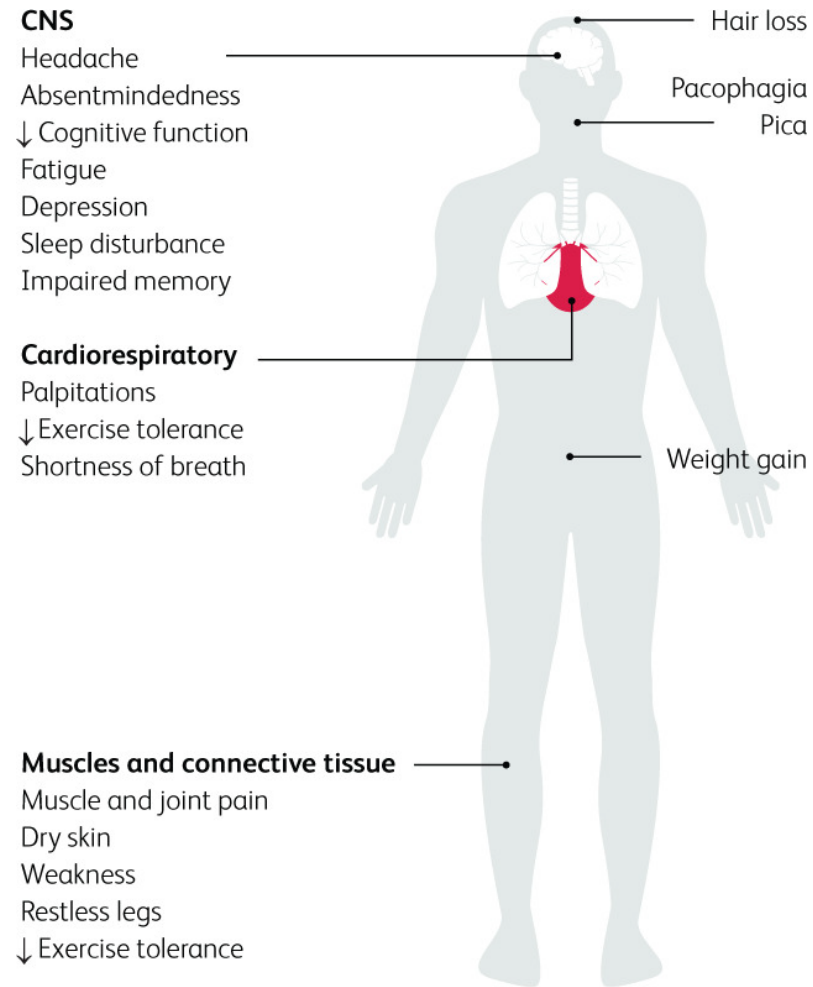
- Erythropoietic effects
 - Maternal anaemia
 - Cardiac failure
 - Fetal anaemia
 - Increased risk of PPH
 - Higher likelihood of requiring transfusion of blood products
 - Transfusion reaction
 - Antibody sensitisation for future pregnancy

Fetal iron deficiency

- Neonates born to iron deficient mothers can have iron deficiency
- Critical threshold is maternal ferritin 10-14 $\mu\text{g/L}$



Consider non-erythropoeitic roles of iron



Iron deficiency without anaemia

- lower birth weight
- Impaired neurocognitive function (poor memory, slower processing)
 - Both mothers and infants
- Depression
 - Post partum iron deficiency is associated with post-partum depression
- mother-infant interactions

Royal College
of Physicians

Clinical Medicine

[Clin Med \(Lond\)](#). 2021 Mar; 21(2): 107–113.

doi: [10.7861/clinmed.2020-0582](https://doi.org/10.7861/clinmed.2020-0582)

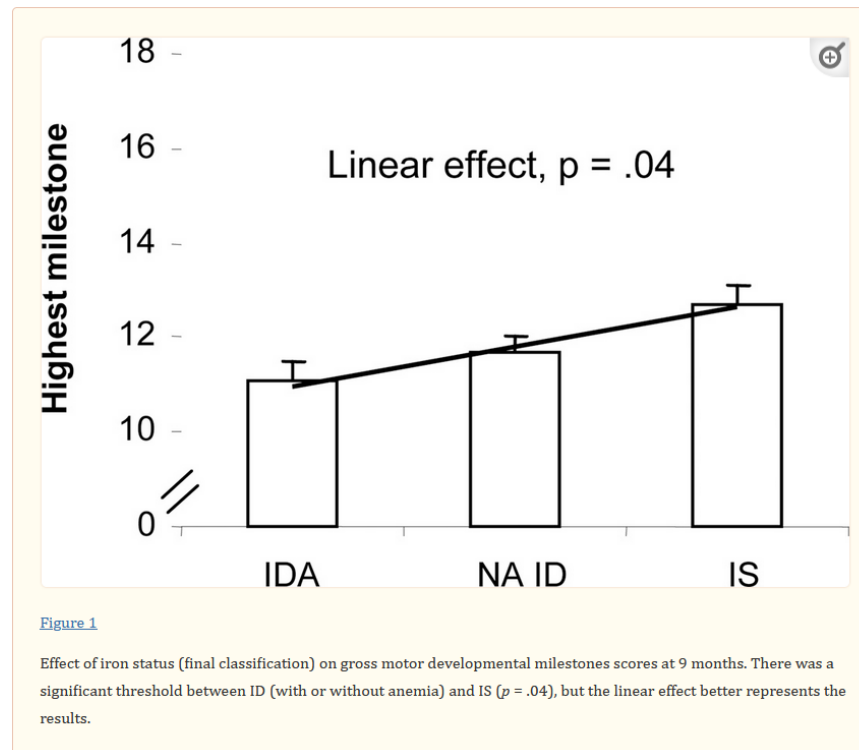
PMCID: PMC8002799

PMID: [33762368](https://pubmed.ncbi.nlm.nih.gov/33762368/)

Iron deficiency without anaemia: a diagnosis that matters

[Abdulrahman Al-Naseem](#), medical student,^A [Abdelrahman Sallam](#), medical student,^A
[Shamim Choudhury](#), medical student,^A and [Jecko Thachil](#), consultant in haematology^B

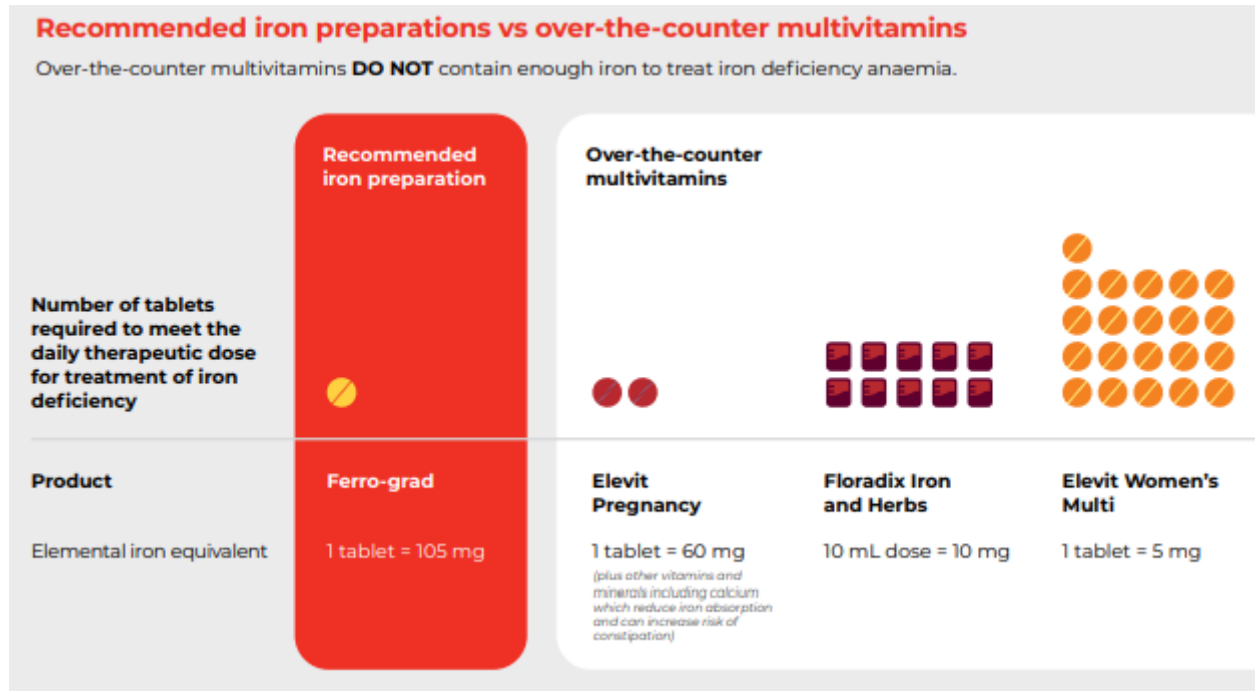
- Many studies looking at adverse effects of **iron sufficiency vs iron deficiency without anaemia vs iron deficiency anaemia**.
- Breakpoint is iron deficiency vs iron sufficiency, rather than anaemia



Oral iron is always first line

	Recommended iron preparations	Elemental iron	Dosage information
53 cents/tablet	<input type="checkbox"/>  Ferro-grad Ferrous sulfate 325 mg tablets	105 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
63 cents/tablet	<input type="checkbox"/>  Ferro-grad C Ferrous sulfate 325 mg tablets	105 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
16 cents/tablet	<input type="checkbox"/>  Ferro-F-Tab Ferrous fumarate 310 mg tablets	100 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
88 cents/tablet	<input type="checkbox"/>  Maltofer Iron polymaltose 370 mg tablets	100 mg per tablet	Take one tablet with food: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
\$1.53 /dose	<input type="checkbox"/>  Maltofer Syrup Iron polymaltose 370 mg/10 mL oral liquid	100 mg/10 mL	Take _____ mL with food, through a straw to avoid staining teeth.
	<input type="checkbox"/>  Ferro-grad F Ferrous sulfate 250 mg tablets	80 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
	<input type="checkbox"/>  Fefol Iron & Folate Supplement Ferrous sulphate 270 mg capsules	87.4 mg per capsule	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
	<input type="checkbox"/>  Ferro-Tab Ferrous fumarate 200 mg tablets	65.7 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
	<input type="checkbox"/>  Ferro-Liquid Ferrous sulphate 30 g/mL oral liquid	60 mg/10 mL	Take _____ mL with food, through a straw to avoid staining teeth.

Minimum 60mg, minimum alternate day dosing



Iron is constipating



How often?



- Following an iron load ... hangs around for 24 hours
- Alternate daily as effective as daily outside of pregnancy, for same number of tablets taken
- In pregnancy time is finite
- Definitely not BD
- Some advocate for double the dose alternate days (small studies)

Intravenous iron is SECOND LINE (T2 and T3)

- Iron deficiency anaemia AND any of the below
 - Failed to respond to oral iron
 - Intolerant of oral iron
 - <4 weeks until delivery
- Special groups to consider
 - Bariatric surgery – unable to absorb PO iron
 - Transfusion is not an option
 - Likelihood of PPH requiring transfusion is high
 - Case by case basis - consultant discussion

Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomized controlled trial (FER-ASAP)

J. Perinat. Med. 2017; 45(4): 443–453

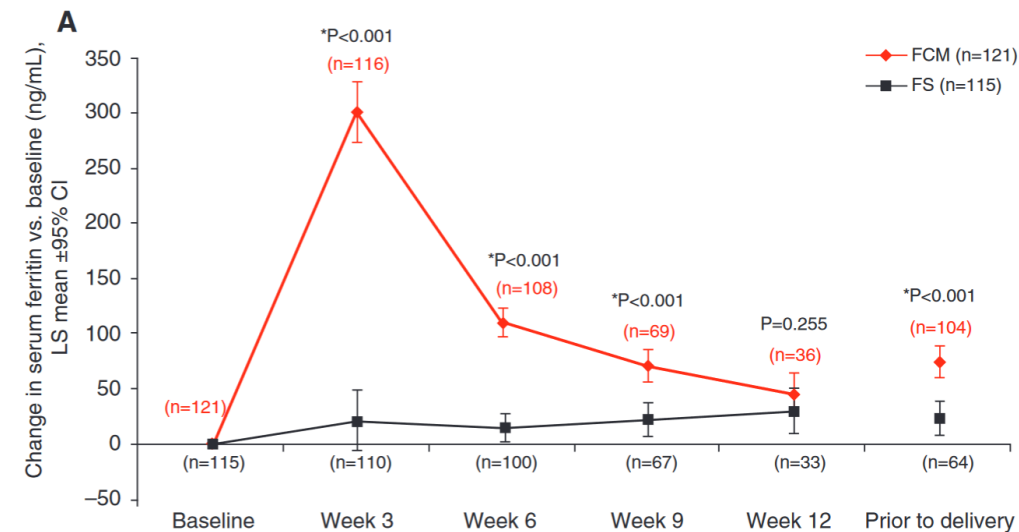


- Treatment related adverse effects were similar between groups
- 11% in the IV iron group vs 15% in the PO group

Table 3: Treatment-related TEAEs by severity.

Treatment-related TEAE severity, number of patients (%)	Ferric carboxymaltose (n=123)	Ferrous sulfate (n=124)
Total	60 (49)	50 (40)
Mild	43 (72)	28 (56)
Moderate	17 (28)	20 (40)
Severe	0 (0)	2 (4)

TEAE=treatment-emergent adverse event.



*Indicates the P value is significant at the $\alpha=0.05$ level

IV iron preparations

- 4 available in Australia
 - ferric carboxymaltose (Ferinject)
 - ferric derisomaltose (Monofer)
 - *iron polymaltose (Ferrosig injection) (IM)*
 - *iron sucrose (Venofer) (dialysis patients)*
- Indication: iron deficiency where oral administration is ineffective or contraindicated; or where there is a need to deliver iron rapidly.

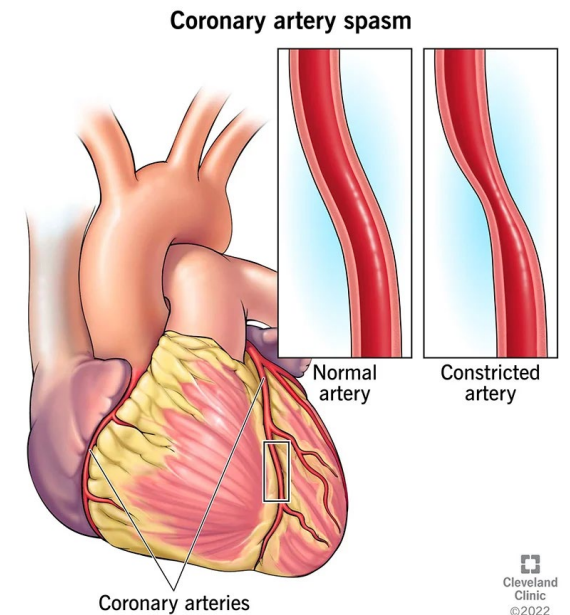


Adverse Reactions

- Hypersensitivity
 - Class effect of all parenteral iron products
 - However true anaphylaxis is very rare with FCM
 - Hypersensitivity may compromise maternal oxygenation
 - This may lead to **fetal hypoxia** and a subsequent compensatory mechanism may result in **fetal bradycardia**
 - TGA Update July 2021

Kounis Syndrome

- “acute allergic coronary syndrome”
- “anaphylactic acute coronary syndrome”
- “allergic angina”
- conditions associated with mast cell activation
 - Allergies
 - hypersensitivity and anaphylactic or anaphylactoid reactions
 - Leads to release of inflammatory mediators
- Inflammatory mediators released during a hypersensitivity reaction



Low Phosphate

- FCM causes mild asymptomatic transient hypophosphataemia
- rare risk of severe, symptomatic hypophosphataemia
- Nadir 2 weeks following infusion, returns to normal by 12 weeks
- Symptoms:
 - muscular symptoms (weakness, asthenia, leading to progressive myopathy including cardiorespiratory compromise and death)
 - neurological symptoms (tingling, altered mental status, seizures, paralysis)
 - haematological changes
 - fatigue
- Risk factors:
 - long-term iron replacement
 - lower baseline ferritin
 - gastrointestinal disorders, malnutrition or other causes of phosphate deficiency (low whole body phosphate).

Skin discolouration

- “iatrogenic cutaneous siderosis”
- Paravenous leakage at the administration site may lead to potentially long lasting brown discolouration and irritation of the skin
- In case of paravenous leakage, the administration must be stopped immediately
- 0.68-1.3%

Fig. Iron stain



Avoid intravenous iron administration via cannulation at sites of flexion (e.g. antecubital fossa, wrist) or on the back of the hand

The distal veins of the forearm are the preferred site

Use an appropriate cannula size (20- to 24-gauge)

Secure the cannula and use an extension set to minimise catheter movement

Do not cover the injection site with a bandage

Minimise the number of cannulation attempts

Ensure the patency of the vein before administration. If patency is uncertain, do not administer intravenous iron

Do not give infusions at night-time

Do not give infusions to patients unable to report symptoms (e.g. anaesthetised)

Analysis of Adverse Events and Intravenous Iron Infusion Formulations in Adults With and Without Prior Infusion Reactions

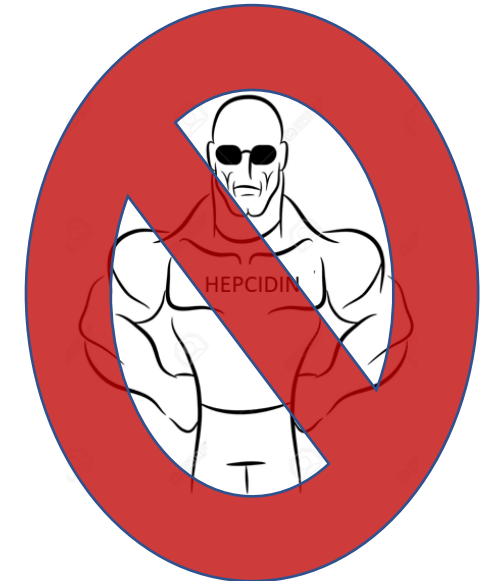
Asad H. Arastu, MD; Benjamin K. Elstrott, BA; Kylee L. Martens, MD; Jonathan L. Cohen, PharmD; Michael H. Oakes, MD; Zhoe T. Rub, MS; Joseph E. Aslan, PhD; Thomas G. DeLoughery, MD; Joseph Shatzel, MD

March 2022

- 35 737 unique iron infusions in 12 237 patients
 - Total infusion events 3.9%
 - 1.4% in FCM
 - Severe adverse events were exceedingly rare
 - 2 documented epinephrine administrations, both associated with iron dextran
 - Higher rates of reaction in those with prior reaction, receiving the same formulation

High ferritin – true overload

- True iron overload – ie Hereditary Haemochromatosis
- Excess iron deposited as haemosiderin
 - Insoluble, cf ferritin
 - End organ damage
 - Takes many years to accumulate
 - Women mostly an issue after menopause
- In pregnancy iron demands are high
- Plentiful iron stores beneficial to woman

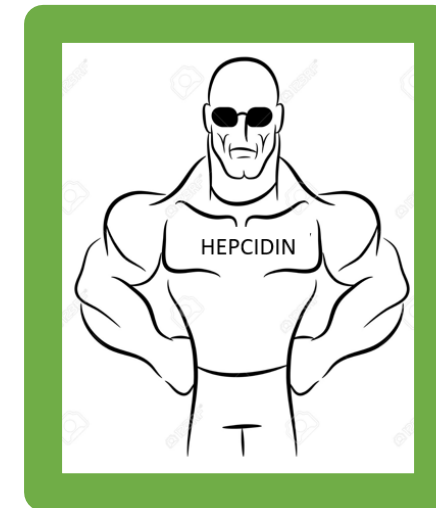


Iron Studies

Iron	H 31.1	umol/L	(5.0 - 30.0)
Transferrin	L 1.6	g/L	(2.0 - 3.2)
TIBC (Calculated)	L 39	umol/L	(46 - 70)
Saturation	H 80	%	(10 - 45)
Ferritin	H 443	ug/L	(30 - 300)
Comment on Lab ID 846493299			

High ferritin - inflammation

- Hyperferritinaemia due to inflammation
 - Normal TSAT
 - Consider underlying source of inflammation
 - Often hepatic steatosis
- Look at Hb, MCV, TSAT
 - Is there evidence of iron restricted erythropoiesis?
 - Iron deficiency can co-exist with high ferritin
 - In this case, PO iron unlikely to be absorbed. Consider IV especially peri-op



IRON STUDIES			
Request Number		25340670	15629827
Date Collected		22 Oct 20	7 Oct 21
Time Collected		10:20	09:43
Specimen Type:	Serum		
Iron (10-30)	umol/L	22	
T'ferrin(27-46)	umol/L	34	
T. Sat. (13-45)		33	
Ferritin(30-400)	ug/L	1729	1865

Case – preconception planning

- ?thalassaemia

Date	08/06/18	09/02/19	07/09/19	18/01/20		
Time F-Fast	0951 F	0912 F	1735 F	Unkn		
Lab ID	289910700	294905516	299487181	843302683	Units	Reference
Ferritin	19	18	L 8	L 12	ug/L	(15-200)

Date	09/02/19	07/09/19	18/01/20	22/06/20		
Time F-Fast	0912 F	1735 F	Unkn	Unkn		
Lab ID	294905516	299487181	843302683	845319960	Units	Reference
Haemoglobin	L 118	L 116	121	130	g/L	(119-160)
RCC	4.7	4.8	4.8	4.9	x10 ¹² /L	(3.8-5.8)
Haematocrit	0.36	0.35	0.36	0.37		(0.35-0.48)
MCV	L 77	L 73	L 74	L 76	fL	(80-100)
MCH	L 25.1	L 24.1	L 25.2	L 26.8	pg	(27.0-32.0)
MCHC	328	330	338	352	g/L	(310-360)
RDW	13.5	14.0	14.0	14.0		(10.0-15.0)
WCC	5.1	5.4	6.8	5.6	x10 ⁹ /L	(4.0-11.0)
Neutrophils	2.80	2.86	3.93	3.13	x10 ⁹ /L	(2.0-7.5)
Lymphocytes	1.71	1.85	2.08	1.64	x10 ⁹ /L	(1.0-4.0)
Monocytes	0.38	0.45	0.47	0.46	x10 ⁹ /L	(0.0-1.0)
Eosinophils	0.20	0.18	0.25	0.29	x10 ⁹ /L	(0.0-0.5)
Basophils	0.04	0.03	0.03	0.04	x10 ⁹ /L	(0.0-0.3)
NRBC	<1.0	<1.0	<1.0	<1.0	/100 WBC	(<1)
Platelets	335	303	298	262	x10 ⁹ /L	(150-450)

- 6 months of oral iron replacement

Iron	16	umol/L	8 - 30
Transferrin	2.9	g/L	1.8 - 3.5
Ferritin	50	ug/L	30 - 150
Transferrin Sat'n	21	%	15 - 45

Haematology

④ Hb (Haemoglobin)	133	g/L	115 - 165
④ Red Cell Count	4.87	10 ¹² /L	3.80 - 5.80
④ Haematocrit	0.398	L/L	0.320 - 0.460
④ MCH	27	pg	27 - 32
④ MCHC	333	g/L	310 - 360
④ MCV	82	fl	80 - 100
④ RDW	14.1	%	< 15.0
④ White Cells	7.7	10 ⁹ /L	4.0 - 11.0
④ Platelets	224	10 ⁹ /L	150 - 400
④ MPV	7.6	fl	7.2 - 11.1
④ Neutrophils	5.1	10 ⁹ /L	2.0 - 8.0
④ Lymphocytes	1.6	10 ⁹ /L	1.0 - 4.0
④ Monocytes	0.5	10 ⁹ /L	0.2 - 1.0
④ Basophils	0.1	10 ⁹ /L	< 0.1
④ Eosinophils	0.4	10 ⁹ /L	< 0.5

normal ranges:

8 - 30
1.8 - 3.5
30 - 150
15 - 45

Iron Studies	
<input type="checkbox"/> Iron	11 umol/L
<input type="checkbox"/> Transferrin	3.0 g/L
<input type="checkbox"/> Ferritin	369 ug/L H
<input type="checkbox"/> Transferrin Saturation (%)	14 % L

EA

Iron Studies	
<input type="checkbox"/> Iron	11 umol/L
<input type="checkbox"/> Transferrin	2.7 g/L
<input type="checkbox"/> Ferritin	22 ug/L L
<input type="checkbox"/> Transferrin Saturation (%)	15 %

CC

Iron Studies	
<input type="checkbox"/> Iron	6 umol/L L
<input type="checkbox"/> Transferrin	2.8 g/L
<input type="checkbox"/> Ferritin	29 ug/L L
<input type="checkbox"/> Transferrin Saturation (%)	8 % L

GB

Iron Studies	
<input type="checkbox"/> Iron	11 umol/L
<input type="checkbox"/> Transferrin	2.9 g/L
<input type="checkbox"/> Ferritin	245 ug/L H
<input type="checkbox"/> Transferrin Saturation (%)	14 % L

Protein Analysis	
<input type="checkbox"/> C-Reactive Protein	19 mg/L H

LA

Iron Studies	
<input type="checkbox"/> Iron	16 umol/L
<input type="checkbox"/> Transferrin	2.9 g/L
<input type="checkbox"/> Ferritin	50 ug/L
<input type="checkbox"/> Transferrin Saturation (%)	21 %

AJ

Iron Studies	
<input type="checkbox"/> Iron	35 umol/L H
<input type="checkbox"/> Transferrin	1.6 g/L L
<input type="checkbox"/> Ferritin	58 ug/L
<input type="checkbox"/> Transferrin Saturation (%)	83 % H

SR

Summary

- Low ferritin = iron deficiency, but normal ferritin doesn't always = iron sufficiency
- Iron deficiency even without anaemia is important in pregnancy
- Oral iron is first line – COUNSEL ON ADMINISTRATION
- IV iron has it's role (second line)
- Risks are low but real - Report any adverse events to TGA