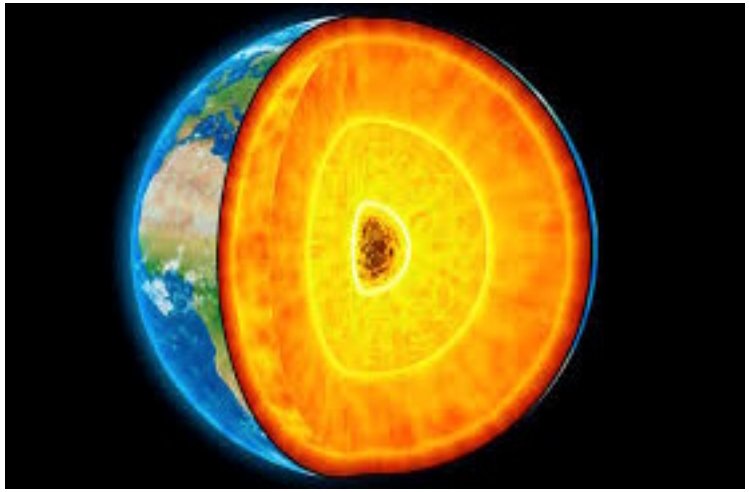
Iron



35% of elements in the planet

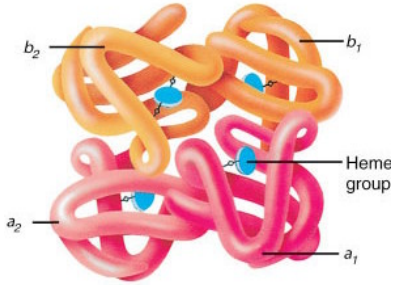
In rock, found oxidised as haematite or magnetite

Iron and the origin of life?

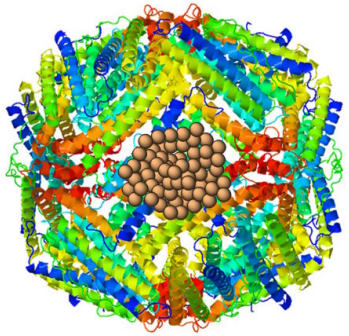
- Iron sulphur clusters may have been central to the earliest life forms 3.5 billion years ago
- Bacterial membranes are minature batteries powered by iron catalyzed reactions
- Mitochondria are intracellular bacteria

Iron in Humans
total = 3-5 grams

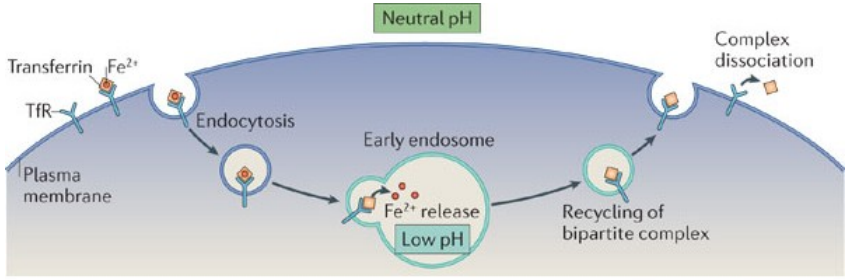
- Hb = 2.7 grams
- MB = 300mg
- Other enzymes = 100mg



- Stores = 0 – 2g in ferritin



- Transferrin bound iron = 3-4 mg



Nature Reviews | Molecular Cell Biology

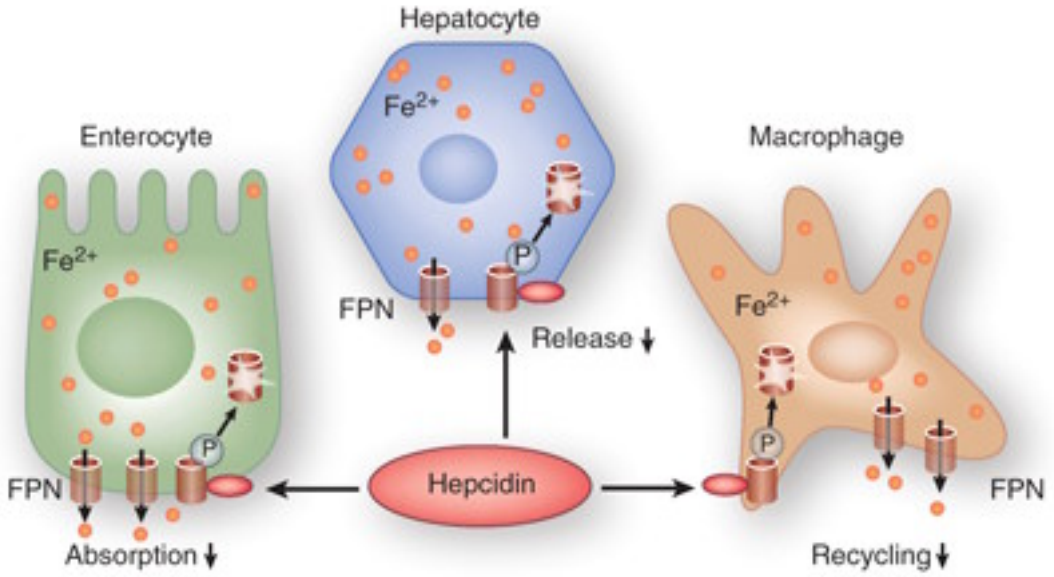
Iron control

Iron can be absorbed but not excreted

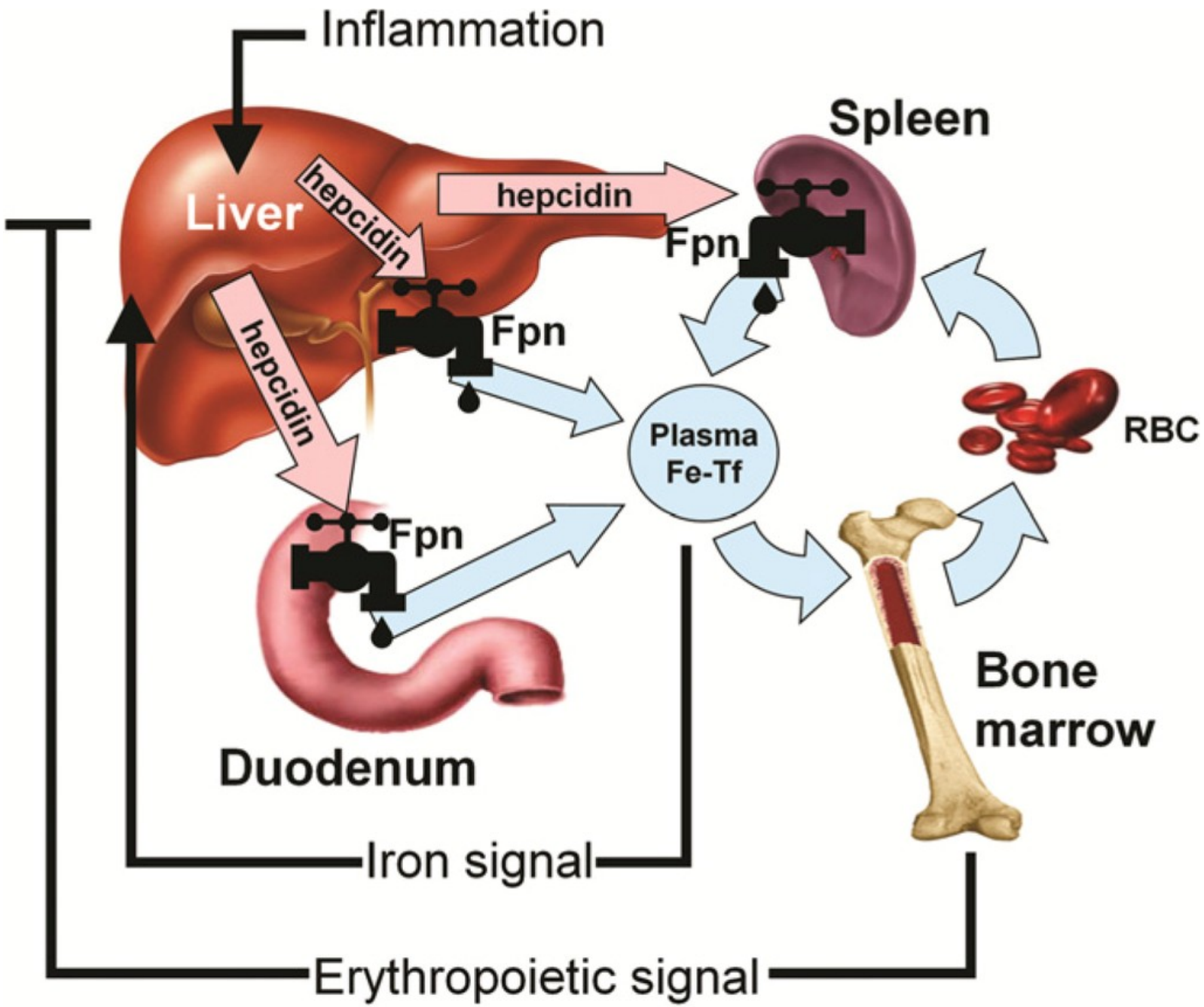
Iron homeostasis is all about controlling absorption and supply

Control	Storage and transport
Ferroportin	Ferritin
Hepcidin	Transferrin
Erythroferrone	

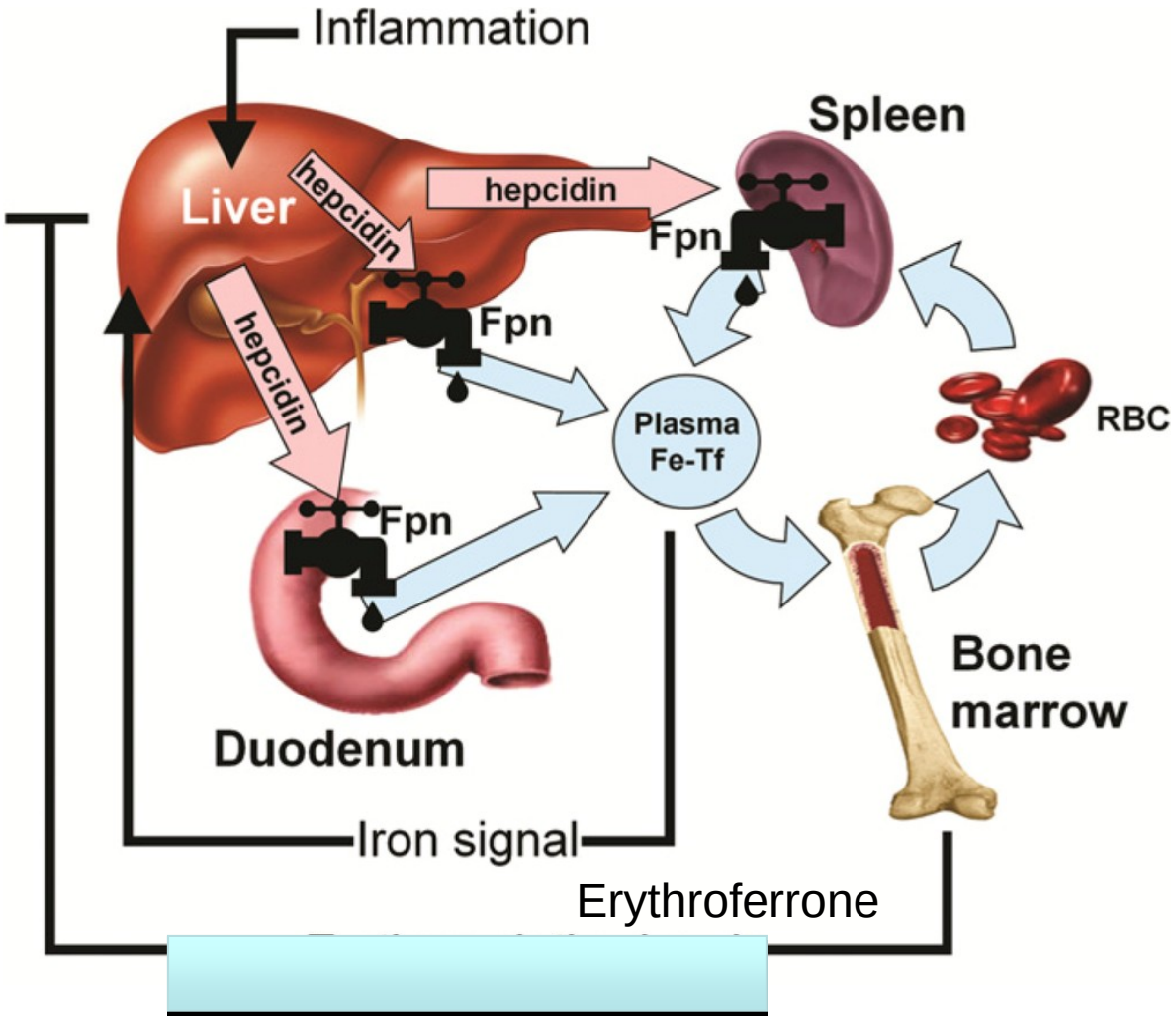
Ferroportin is the channel through which iron crosses membranes



Hepcidin responds to imflammation and destroys ferroportin


Inflammation
Liver
hepcidin
hepcidin
hepcidin
Spleen
Fpn
Fpn
Fpn
Plasma
Fe-Tf
RBC
Bone
marrow
Duodenum
Iron signal
Erythropoietic signal

Kautz, Léon, et al. "Identification of erythroferrone as an erythroid regulator of iron metabolism." *Nature genetics* (2014).



Iron restricted erythropoiesis

Iron deficiency

Deficient iron utilisation

Iron deficiency

Diagnosis

- Hb + MCV/MCH
- ~~Iron and transferrin saturation~~
- Ferritin
- ~~Free Erythrocyte protoporphyrin~~
- ~~Serum Transferrin receptor~~
- ~~Hepcidin~~

Iron deficiency

Ferritin…. what level?

- <12ug/L = definite deficiency
- <20ug/L = depleted stores
- <30ug/L = possible benefit from iron replacement?
- <100ug/L = possible deficiency in inflammation

BUT IS THERE A HAEMOGLOBIN DEFICIT??

Iron in Red Cells

- 1 ml of red cells contains approx 1 mg of Iron
- 1 unit of red cells = 10g/L Hb = 180mg iron

Total body iron?

a. Hb + stores Iron gap =Hb deficit –ferritin
b. 10g/L Hb =~ 20ug/L ferritin
c. Ferritin of 20ug/L = adequate everyday reserves

Example

1. Hb Actual 80g/L Expected 130g/L Deficit 50g/L
2. Ferritin 60ug/L (surplus = 40ug/L) =~ 20g/L Hb
3. Iron deficit = 30g/L Hb = 540mg iron

Deficient iron utilisation

Inflammation/Infection/Cancer

Increased Hepcidin

Iron supplies to red cells reduced

Transferrin reduced

Transferrin saturation much reduced

Ferritin increased up to 3 fold

Fibrinogen/ESR/CRP increased

Iron deficiency and infection

Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial.

Sazawal et al

Lancet. 2006 Jan 14; 367(9505):133-43.

24,000 chilren randomised to supplementation or not.

Trial stopped because of excess hospital admissions and mortality in the treatment arm

Iron and infection

Sazawal et al: further analysis. Children who were iron deficient and were on supplementation did not have a higher admission/mortality

Other studies less certain

Is infection in haemodialysis patients associated with iron overload?

Mixed findings , probably not

Iron and cancer

Beguin, Yves, et al. "Epidemiological and nonclinical studies investigating effects of iron in carcinogenesis—A critical review." *Critical reviews in oncology/hematology* 89.1 (2014): 1-15.

Human data, mainly based on cases after i.m. injection of iron dextran and populations with chronic iron overload, suggest a correlation between chronically increased iron levels and increased cancer risk.

Animal models, mainly based on non-intravenous administration of extremely high cumulative iron doses in iron-replete recipients, suggest that iron overload can promote tumor growth.

Overall, data from epidemiological and nonclinical studies are often conflicting and extrapolation to the clinical setting aiming for normalization of hemoglobin (around 12 g/dL) is difficult.

In the absence of long-term pharmacovigilance studies, iron treatment to prevent or manage chemotherapy-induced anemia should be limited to the time of cytotoxic anti-tumor treatment and iron status should be closely monitored (target TSAT range 20–50%).

Measuring Iron

- Transferrin bound Iron represents that available for use
- Transferrin saturation correlates with storage iron except in any illness with any inflammation
- Ferritin correlates well with storage iron but is relatively increased in severe inflammation

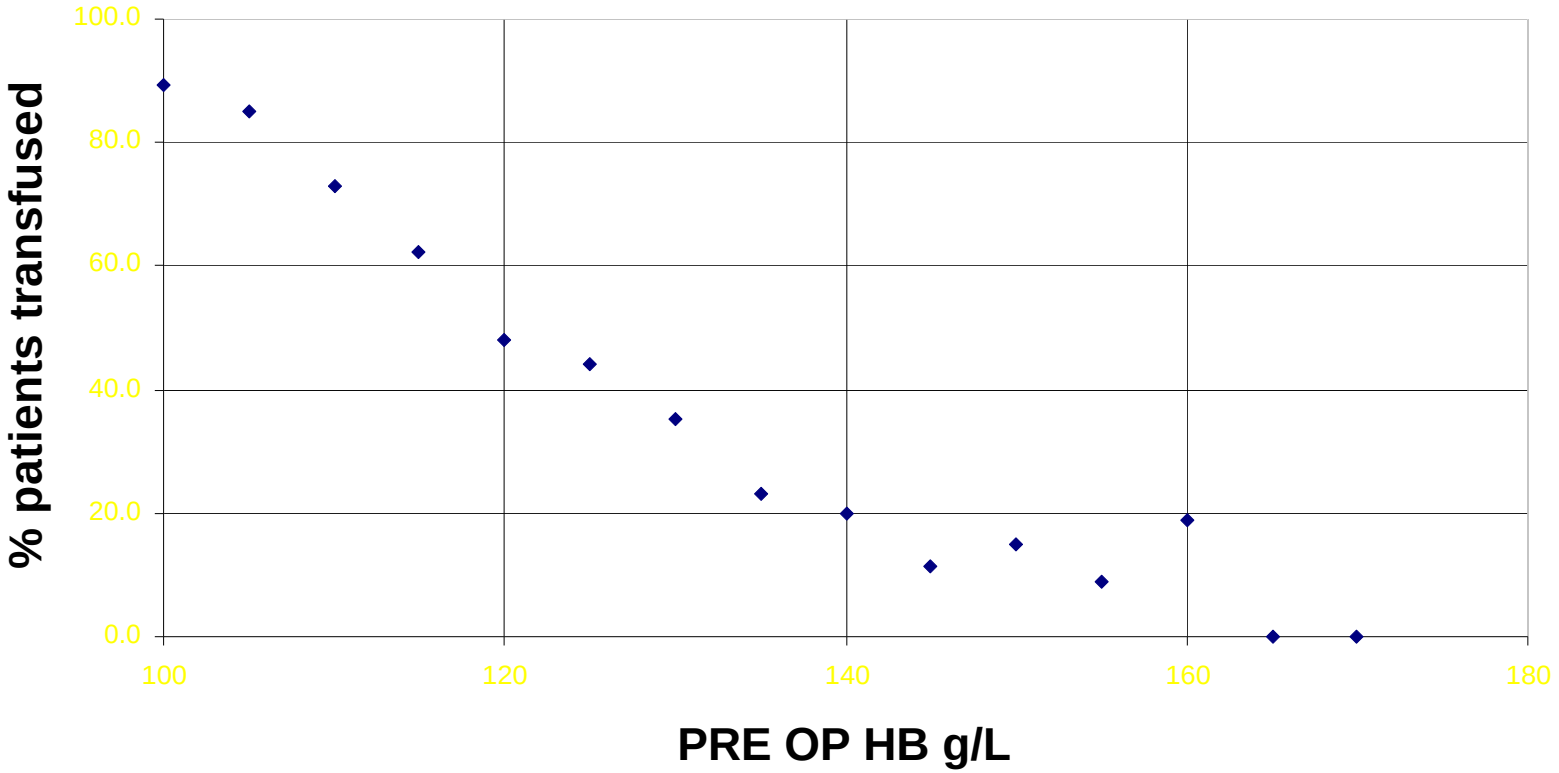
Measuring Iron

- Ferritin is the best measure of iron stores
- Needs correlation with Hb and inflammation

- Transferrin saturation *and* ferritin indicate iron availability

- Hepcidin and other novel markers may become useful in the future for delineating anaemia of chronic disease

Pre-op Hb versus liklihood of transfusion 700 pts THR Freeman Hospital



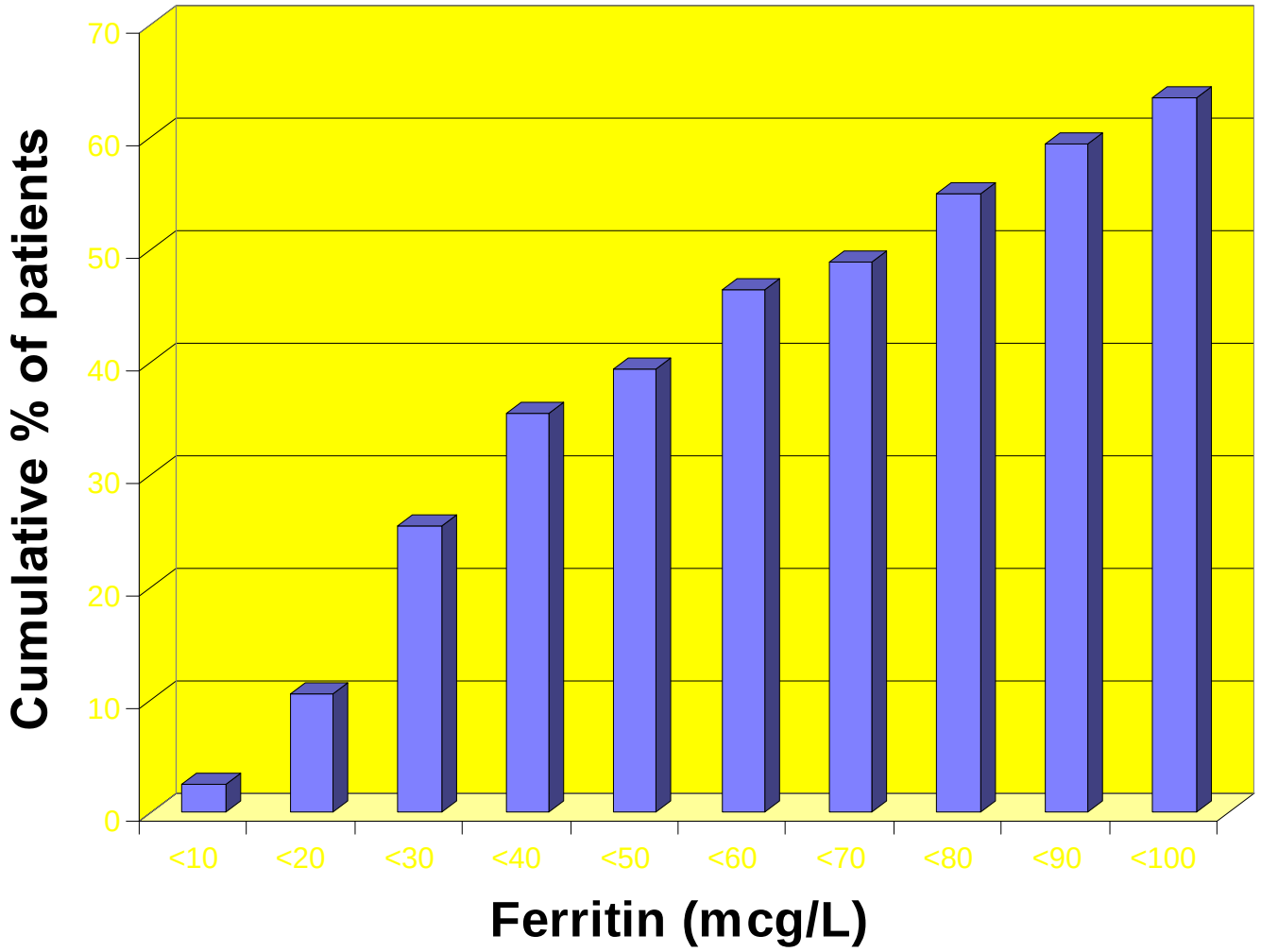
Independent Preoperative variables affecting likelihood of transfusion

Haemoglobin	Yes
Patient Weight	Yes
Age	No
Sex	No
Disease	No

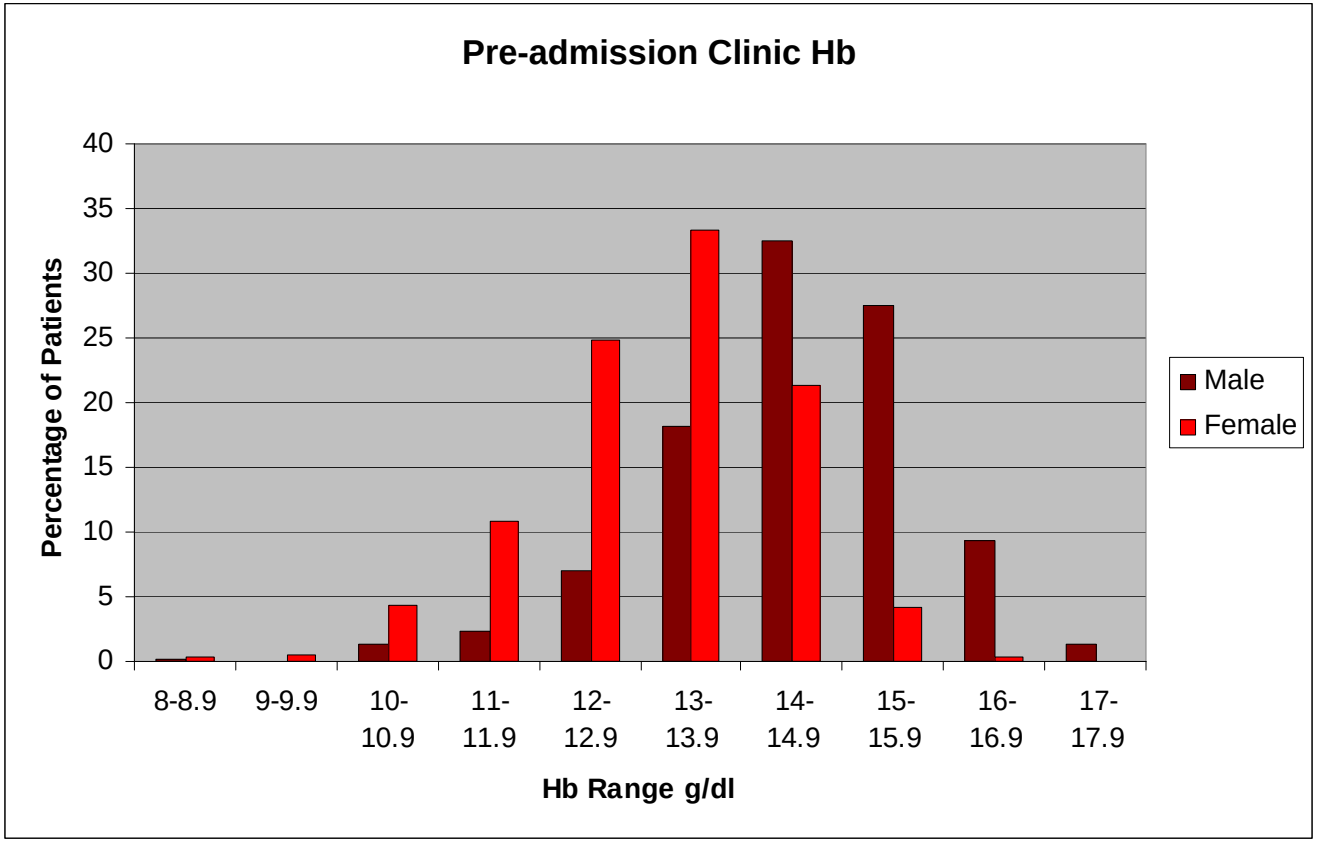
‘Treating reversible anaemia preoperatively will reduce the need for blood transfusion’

What would you like to know?

Ferritin of 225 patients for THR or TKR

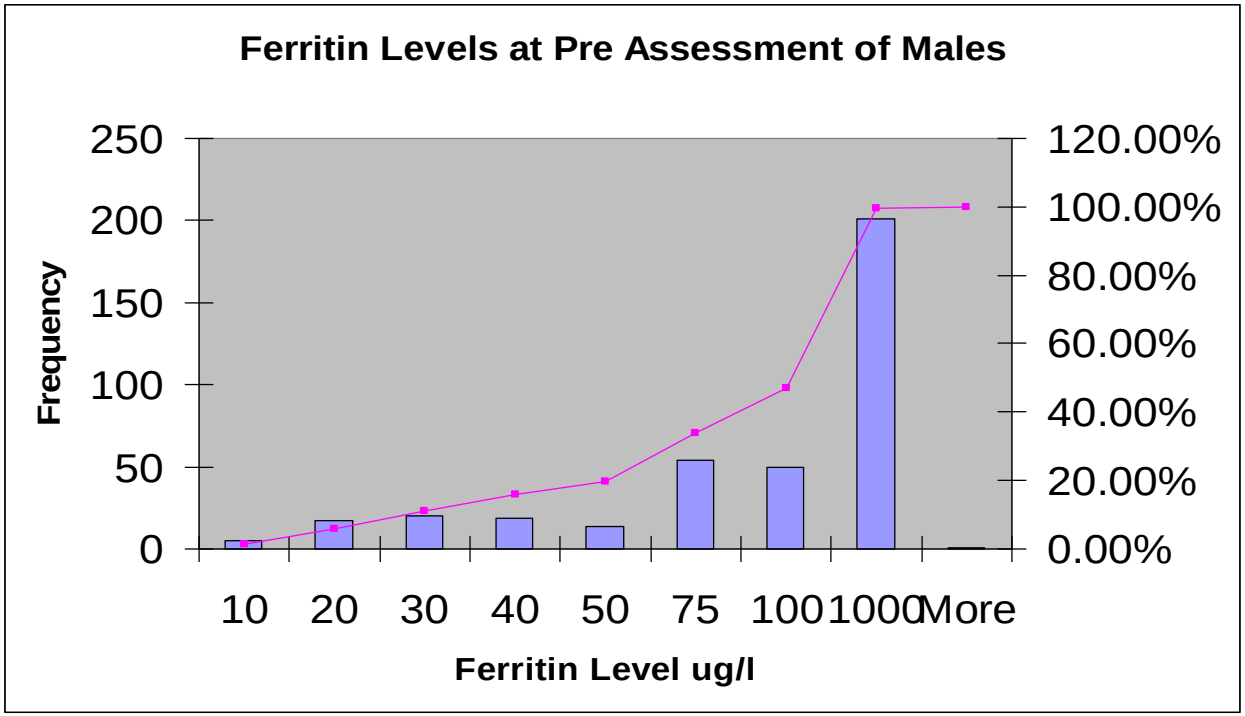


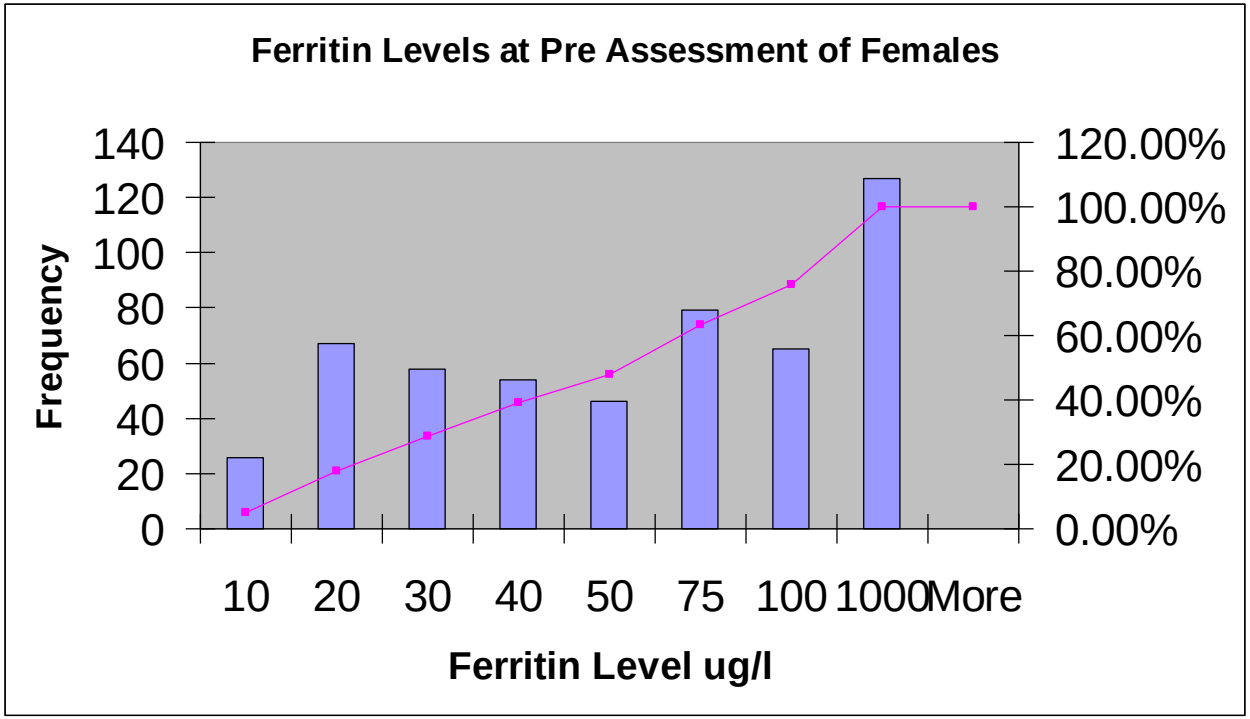
900 orthopaedic surgery patients at Freeman Hospital 2008
Sara Avery *et al*

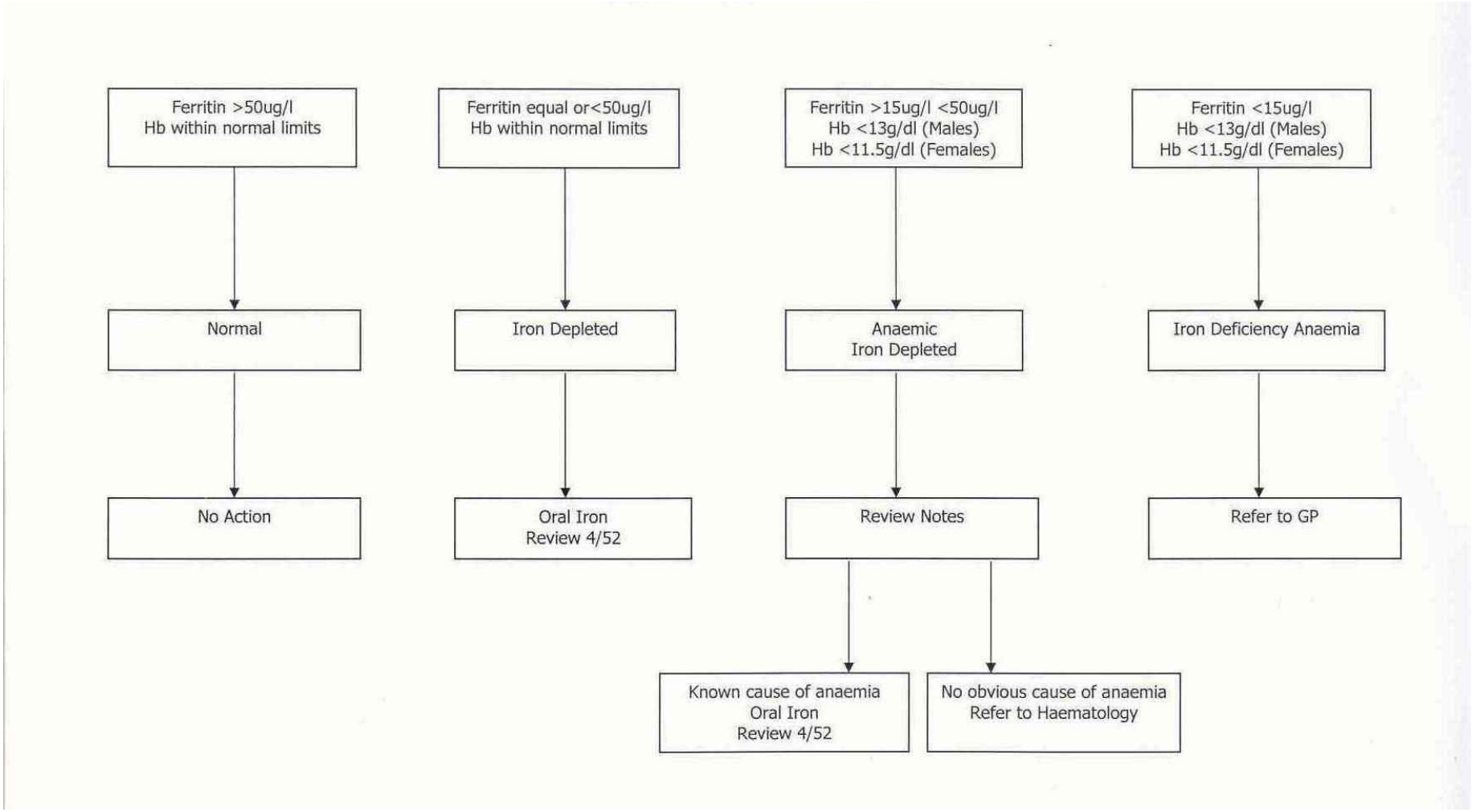


Approx 11% of Men Hb < 130g/L

Approx 15% of Women Hb < 120g/L

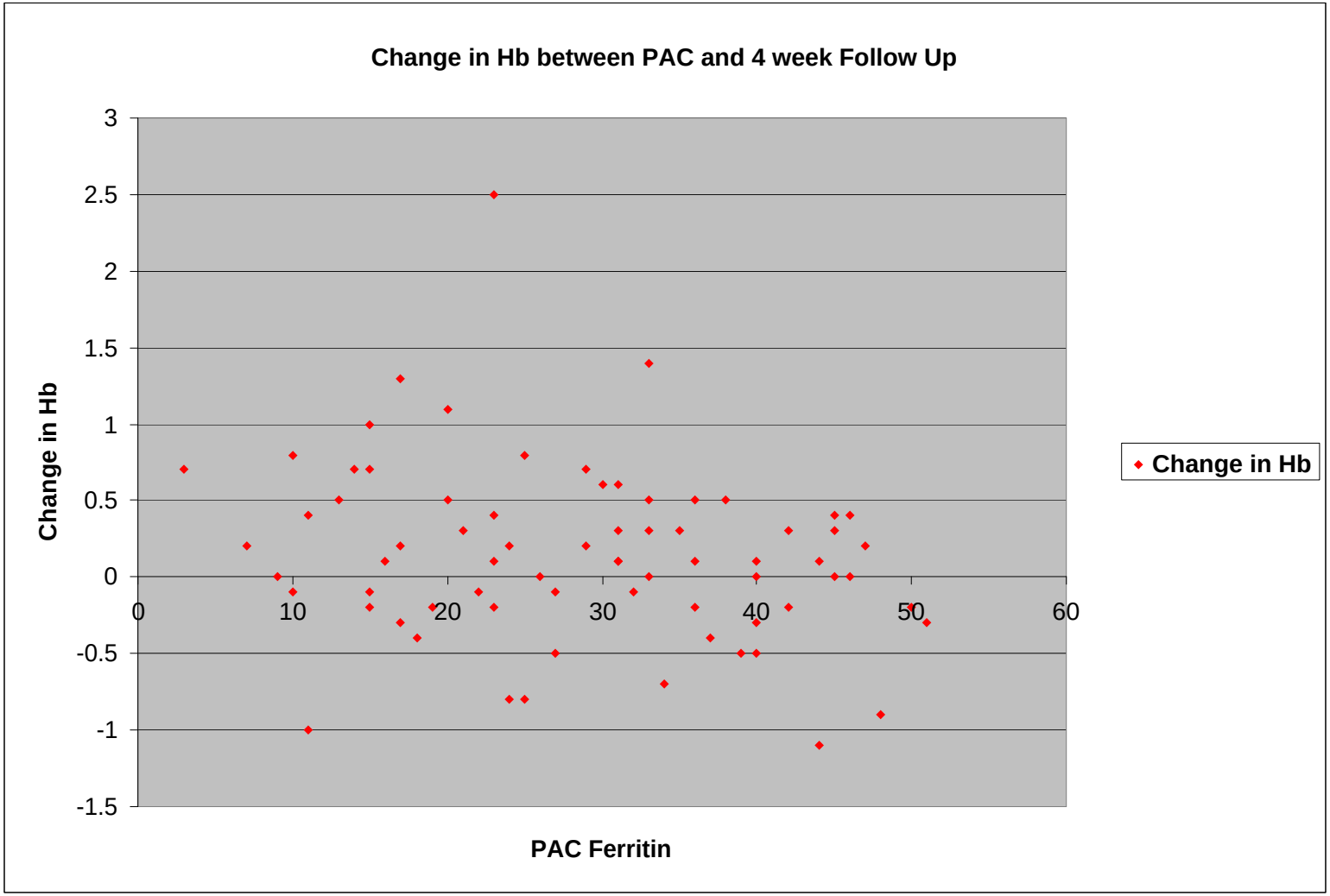

Ferritin Levels at Pre Assessment of Males
Frequency
250
200
150
100
50
0
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
10
20
30
40
50
75
100
1000
More
Ferritin Level ug/l


Ferritin Levels at Pre Assessment of Females
Frequency
140
120
100
80
60
40
20
0
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
10
20
30
40
50
75
100
1000
More
Ferritin Level ug/l

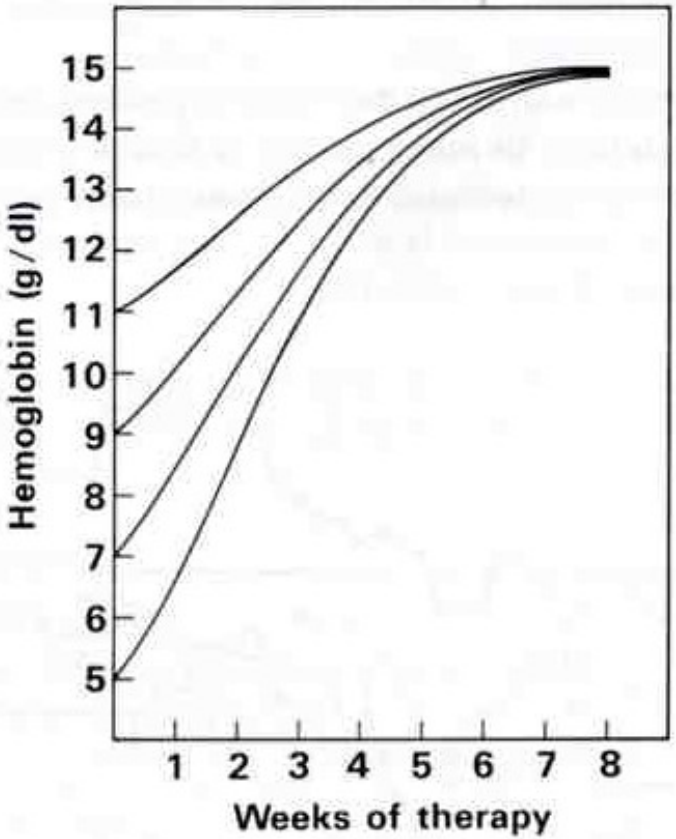

Ferritin >50ug/l
Hb within normal limits
Normal
No Action
Ferritin equal or<50ug/l
Hb within normal limits
Iron Depleted
Oral Iron
Review 4/52
Ferritin >15ug/l <50ug/l
Hb <13g/dl (Males)
Hb <11.5g/dl (Females)
Anaemic
Iron Depleted
Review Notes
Known cause of anaemia
Oral Iron
Review 4/52
No obvious cause of anaemia
Refer to Haematology
Ferritin <15ug/l
Hb <13g/dl (Males)
Hb <11.5g/dl (Females)
Iron Deficiency Anaemia
Refer to GP

14 pts referred back to GP with clearcut Iron deficency anaemia

Other Patients with Ferritin < 50ug/L Rx Ferrous Gluconate 300mg BD



Correction of iron deficiency



<u>Optimal oral iron</u>

Correction of Hb

50% by 18 days

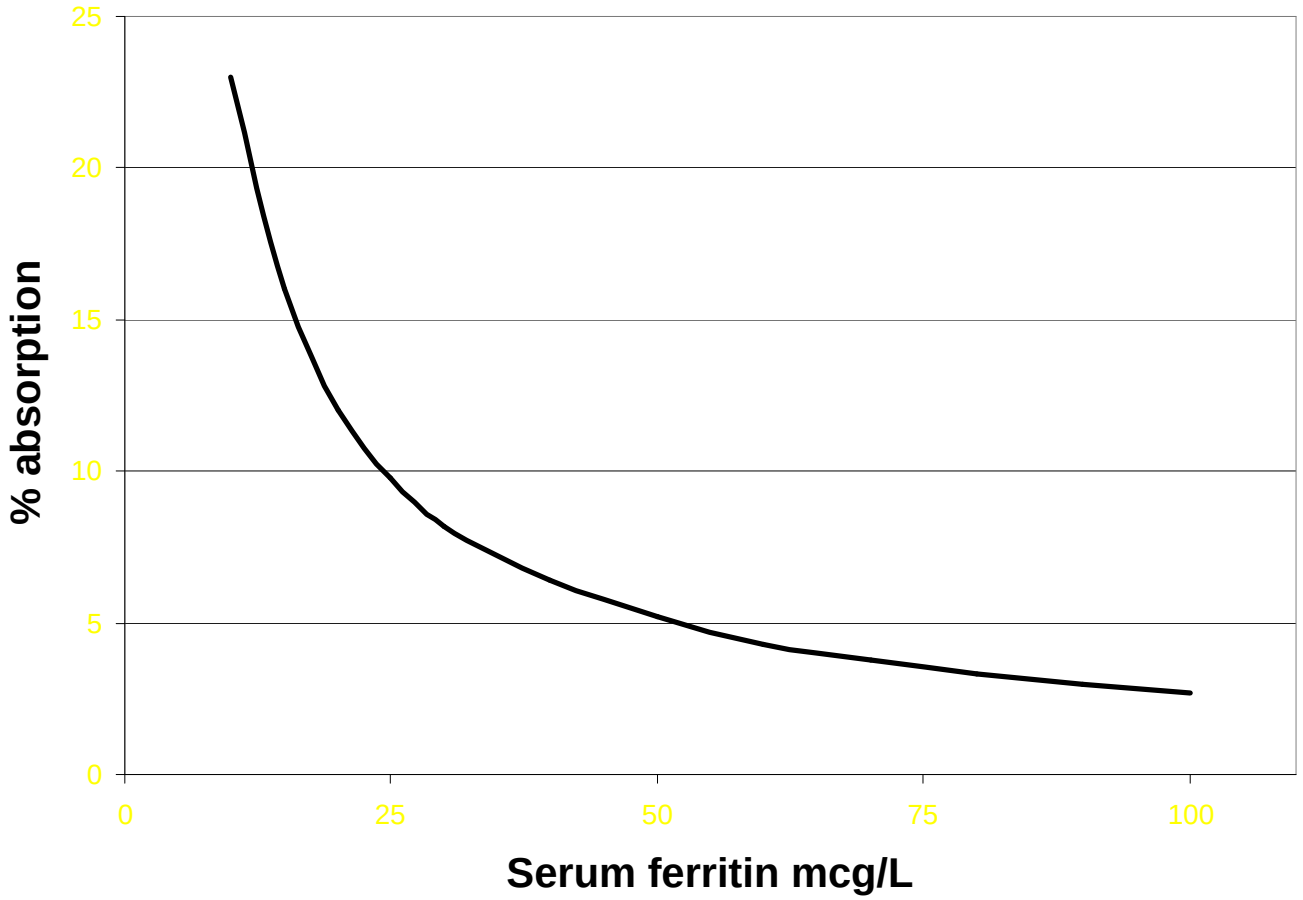
2/3rds by 4 wks

100% by 8 weeks

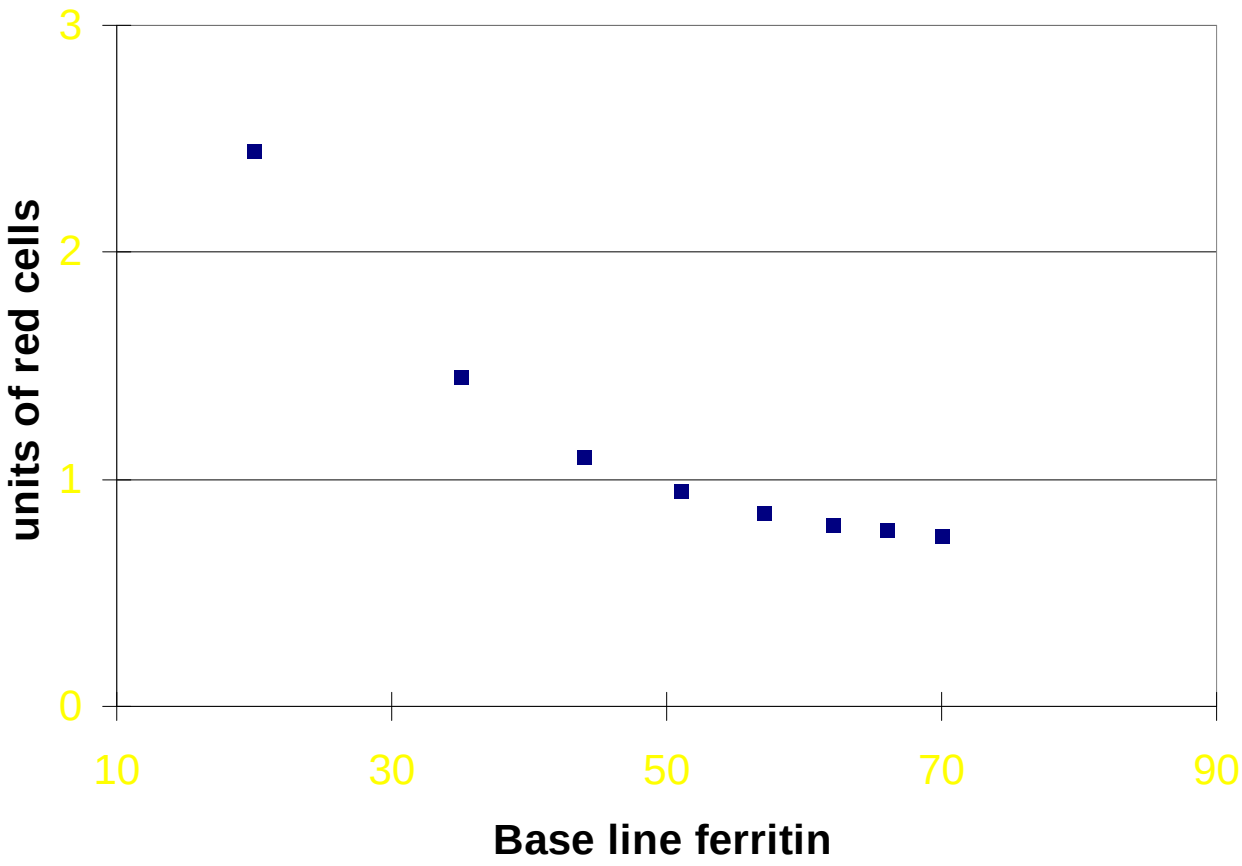
From Wintobe 9th ed

Relationship between serum ferritin and nonheme iron absorption

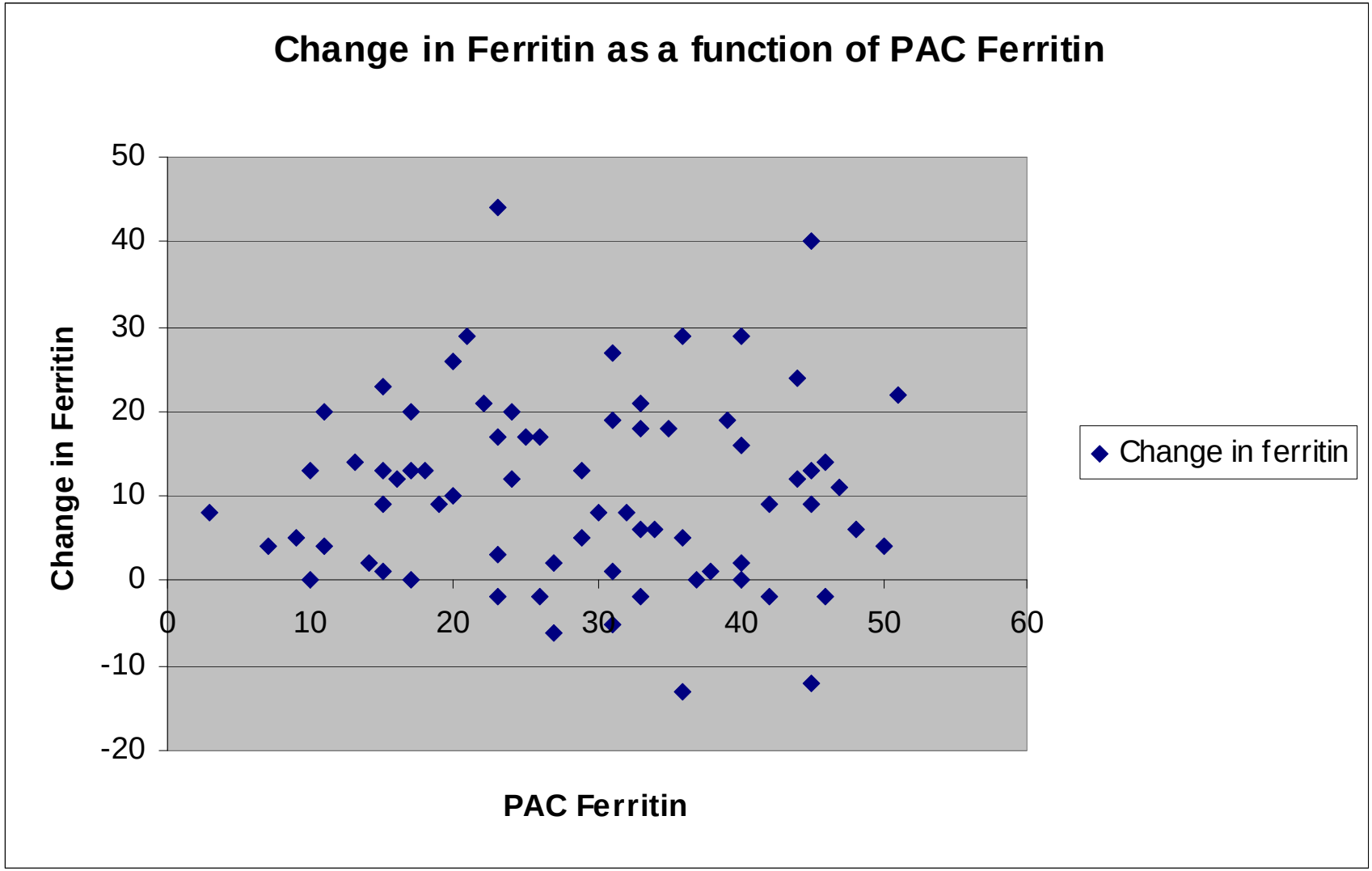
Adapted from Lynch et al.,1989 Blood 74;2187-93



Iron absorption as units of red cells after 28 days $FeSO_4$ tds

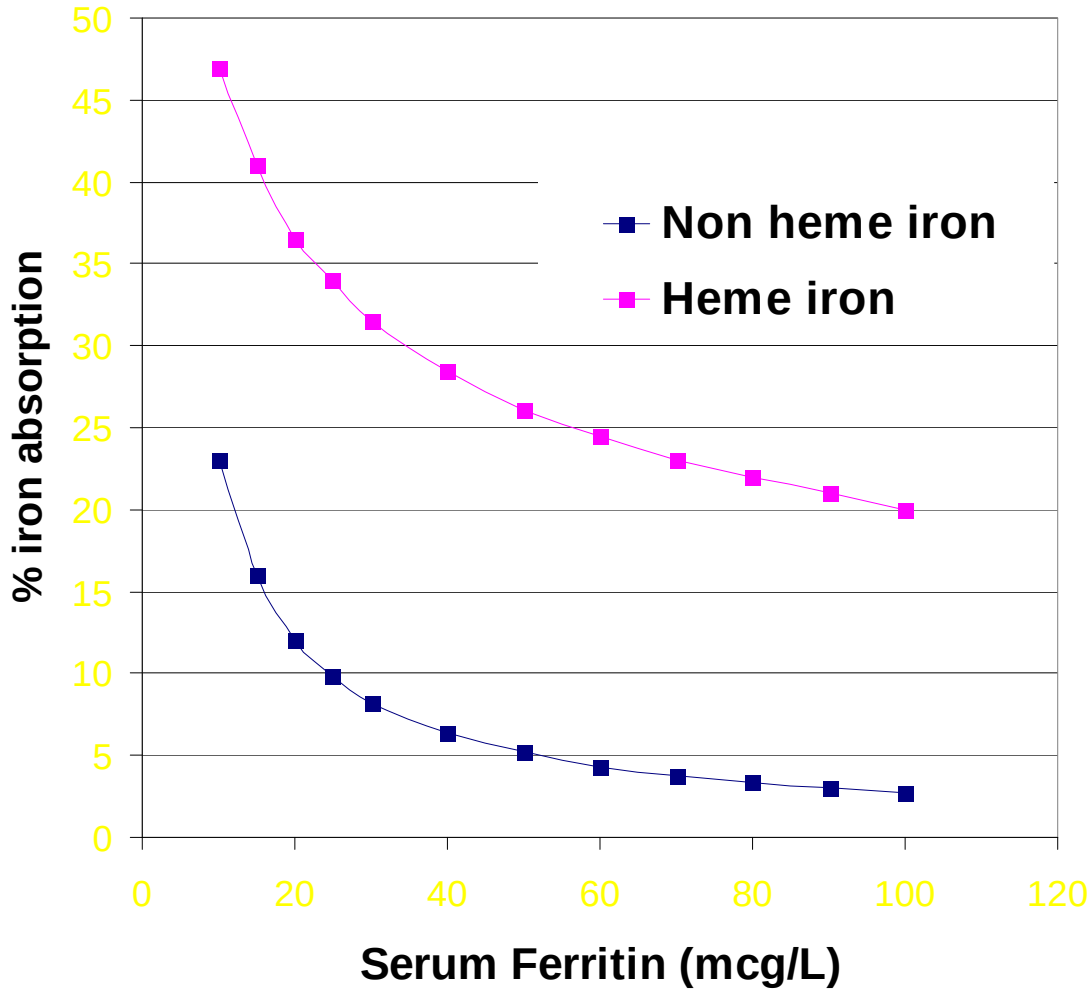


Sara's study showed small increase in ferritin after 4 wks low dose oral iron



Relationship between serum ferritin, heme iron and nonheme iron absorption

Adapted from Lynch et al.,1989 Blood 74;2187-93



Preoperative oral iron supplements

1. Important in iron deficient anaemia

2. Possible benefit in those with ferritin <30µg/L

3. Little benefit in patients with ferritin >30µg/L

Conclusions

1. Haemoglobin and ferritin are the best markers for body iron status

2. Pre-operative Hb is the most important variable that predicts for peri-operative transfusion

3. Treat correctable anaemia eg iron deficiency

4. Oral iron: Post-operative Rx more effective than Pre-operative Rx in those with Ferritin >30 µg/L

5. IV iron: may have a role pre-operatively. ?await results of PREVENT trial and others