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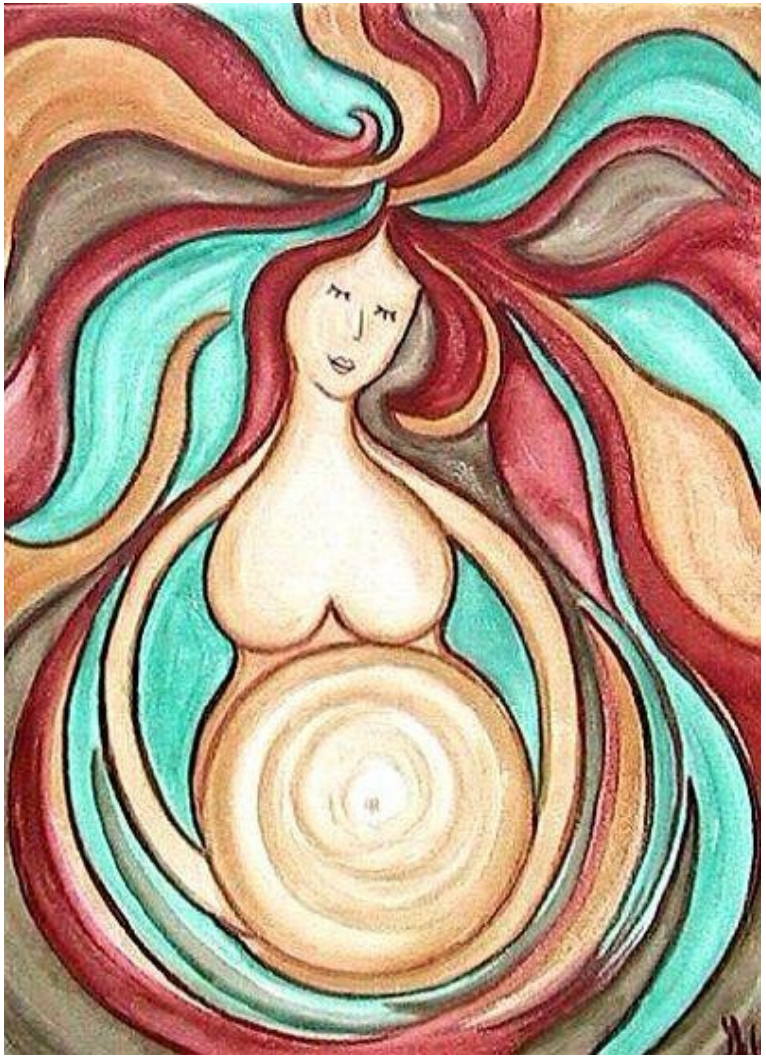
Ironing out the Problem

UK guidelines on iron deficiency in pregnancy



Dr Sue Pavord
Consultant Haematologist
Associate Senior Lecturer in Medicine
Oxford

UK guidelines

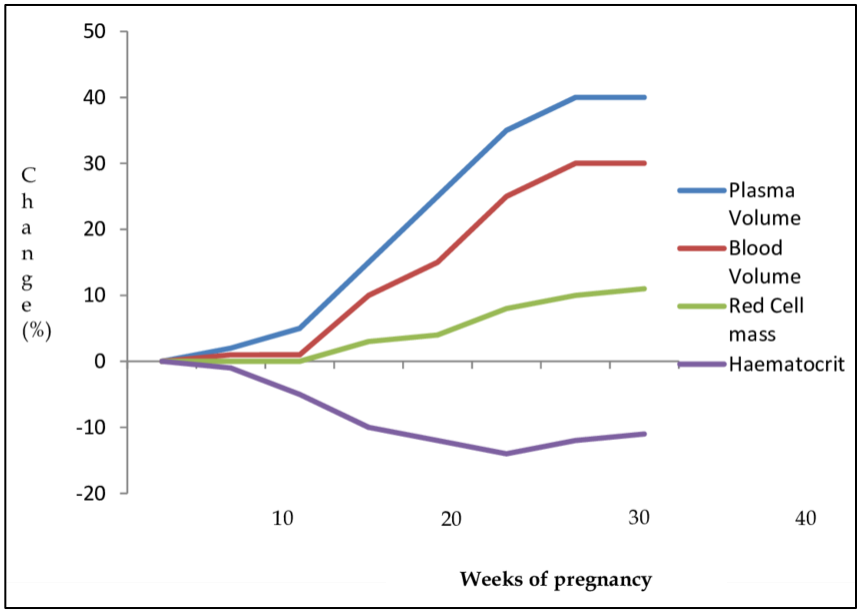
- Definition and prevalence of anaemia
- Effects of ID on mother and baby
- Identification of iron depleted women
- Management of ID
- Prevention

Normal physiological changes

	Non-pregnant	20 weeks	30 weeks	40 weeks
Plasma volume (ml)	2,600	3,150	3,750	3,850
Red cell mass (ml)	1,400	1,450	1,550	1,650
Total blood volume(ml)	4,000	4,600	5,300	5,500
HCT	35	32	30	30

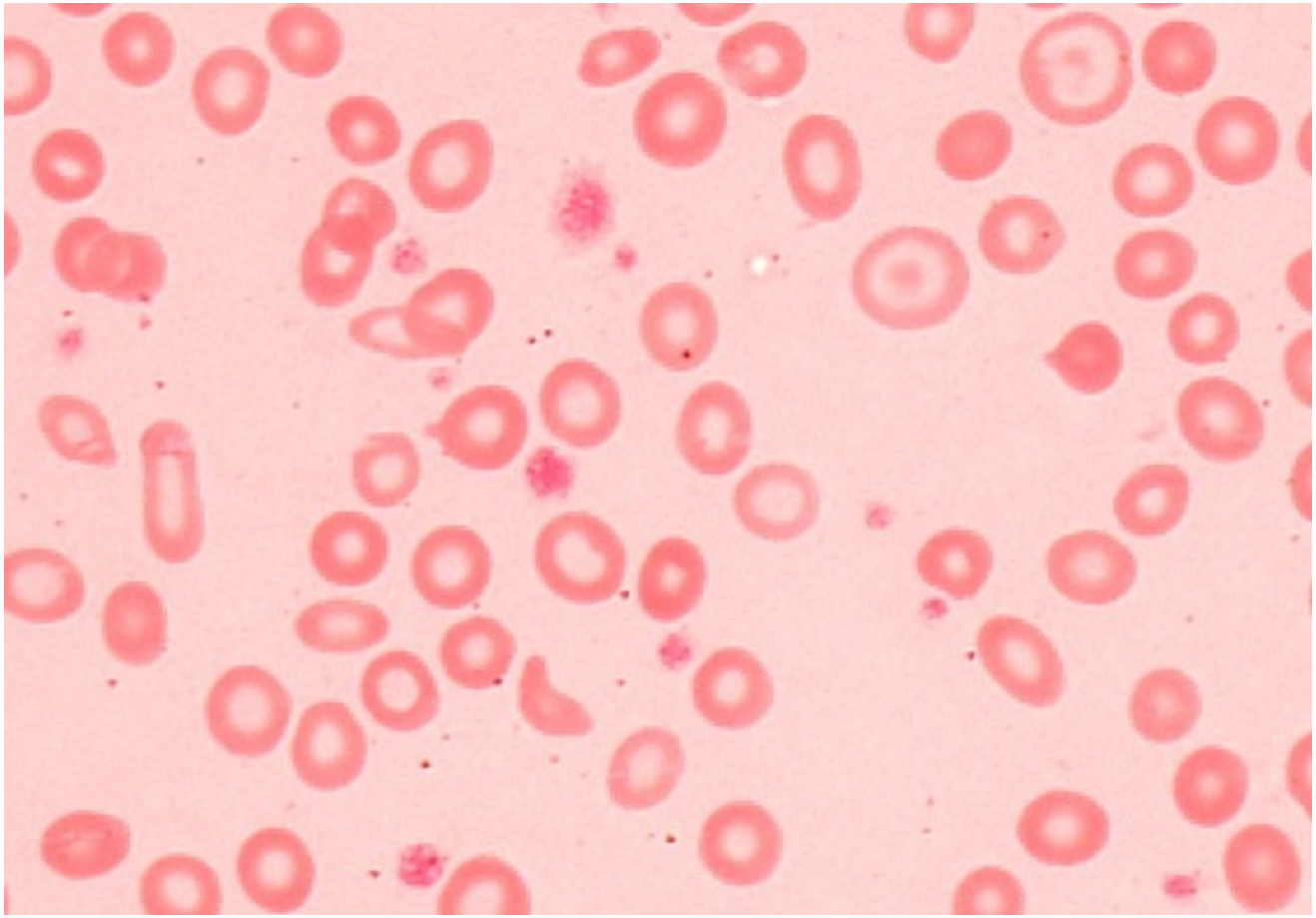
Anaemia – definition

- 1st Trimester <110g/l
- 2nd and 3rd Trimesters <105g/l
- Postpartum <100g/l
- >48 hrs pp <120g/l



World Health Organization Centre for Disease Control and Prevention
British Committee for Standards in Haematology
Figure: Ezechi O, Kalejaiye O. Management of Anaemia in Pregnancy. In *Anemia*, Donald S. Silverberg (Ed). IntechOpen, 2012: pp. 233–46.
Available from: https://www.intechopen.com/books/anemia/management-of-anaemia-in-pregnancy

Iron deficiency



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Increased iron requirements in pregnancy

Source of increased iron requirement	Iron demand
Increased red cell mass	450 mg
Fetus and placenta	300 mg
Increased basal maternal requirements	240 mg
Blood loss at delivery (normal vaginal delivery)	250 mg
EXTRA total iron requirements for pregnancy, labour and delivery	**1240 mg**

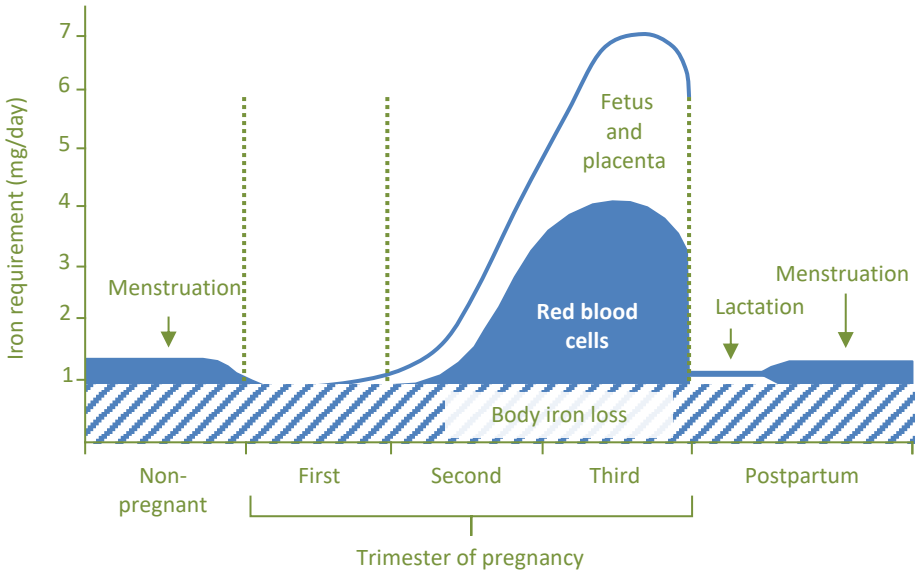

Table from Pavord S, Hunt B. The Obstetric Hematology Manual, Cambridge University Press 2010; Figure adapted from Bothwell TH. *Am J Clin Nutr* 2000;72:S257–S264

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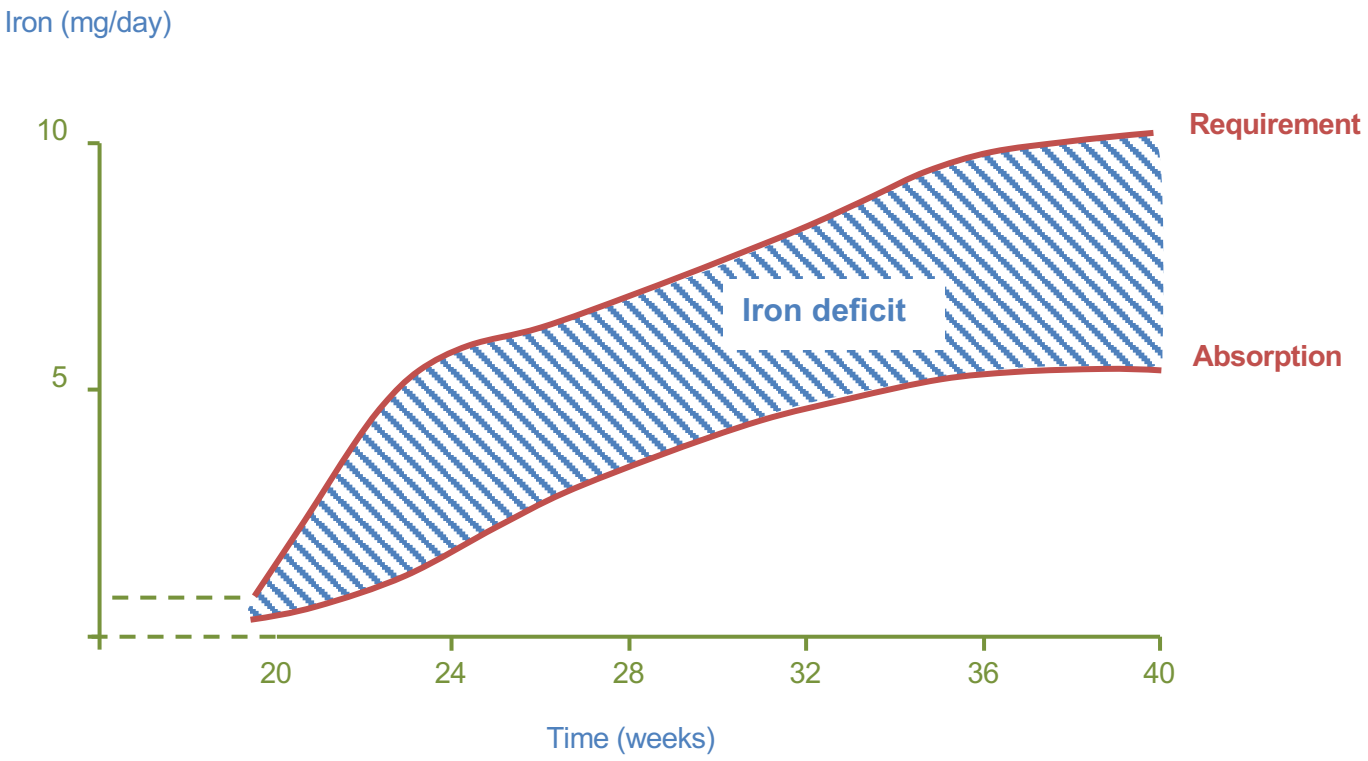
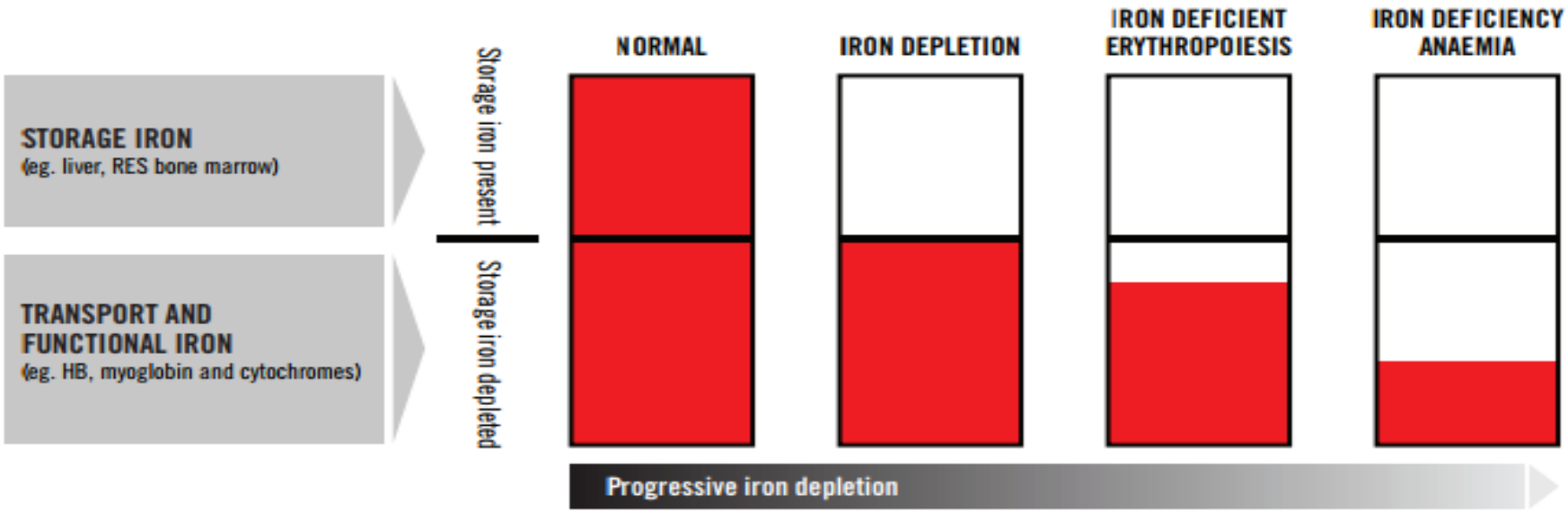
Iron deficit increases during pregnancy

The iron deficit during pregnancy has to be compensated by **iron mobilisation from stores** or by **iron supplementation**



Hallberg L. Nutritional anemias. New York: Raven Press, 1992: pp. 13–28

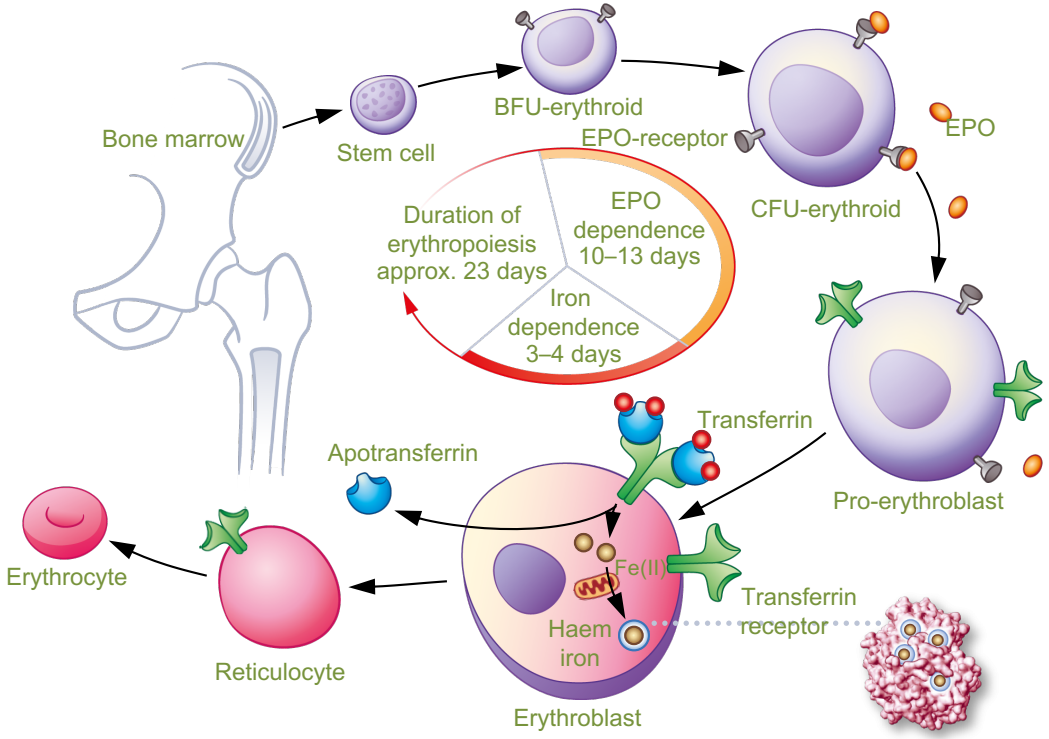
SPECTRUM OF IRON DEFICIENCY



Modified with permission from Sarah Cusick PhD, Centers for Disease Control and Prevention, 2008

Iron depletion	✔ Ferritin levels decrease as body stores become depleted. ✔ Transferrin saturation (reflecting iron transport capacity), declines. ✔ Total iron binding capacity (the number of available sites for transferrin to bind iron) increases.
Iron deficient erythropoiesis	✔ Iron available for red cell production is limited. The haemoglobin (Hb) is within normal range but may be lower than the person's usual Hb. ✔ Red cells distribution width (RDW) increases as red cells will vary in size. ✔ Mean cell haemoglobin (MCH) and mean cell volume (MCV) are usually still in the normal range, but may have fallen from usual level for that individual.
Iron deficiency anaemia	✔ Red cell production is reduced resulting in low Hb, MCH and then MCV. ✔ As Hb progressively decreases, abnormal red cells such as elliptocytes and pencil cells may appear on the blood film.

Production of red blood cells



Haem is needed for the synthesis of Hb, which is the oxygen carrier in RBCs

60–70% of body iron is found in Hb

BFU, burst-forming unit; CFU, colony-forming unit; EPO, erythropoietin; Hb, haemoglobin; RBC, red blood cell
Figure adapted from Besarab A *et al. Oncologist* 2009;14(Suppl 1):22–33; Geissler C, Singh M. *Nutrients* 2011;3:283–316

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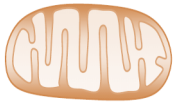
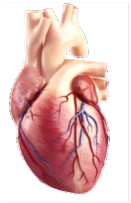
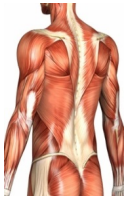
Importance of iron for functioning and survival

Iron is critical for optimal functioning and survival







ID results in:

- Mitochondrial dysfunction
- Deranged activity of enzymes
- Abnormal transport and structural proteins
- Apoptosis

- Tissue remodelling
- Impaired organ efficacy

- Impaired exercise capacity
- Reduced work efficacy
- Impaired cognitive performance and behaviour
- Increased morbidity and mortality

Cells

Tissues

Organs

Body

Population

ID, iron deficiency
Adapted from Jankowska EA *et al. Eur Heart J* 2013;34:816–29

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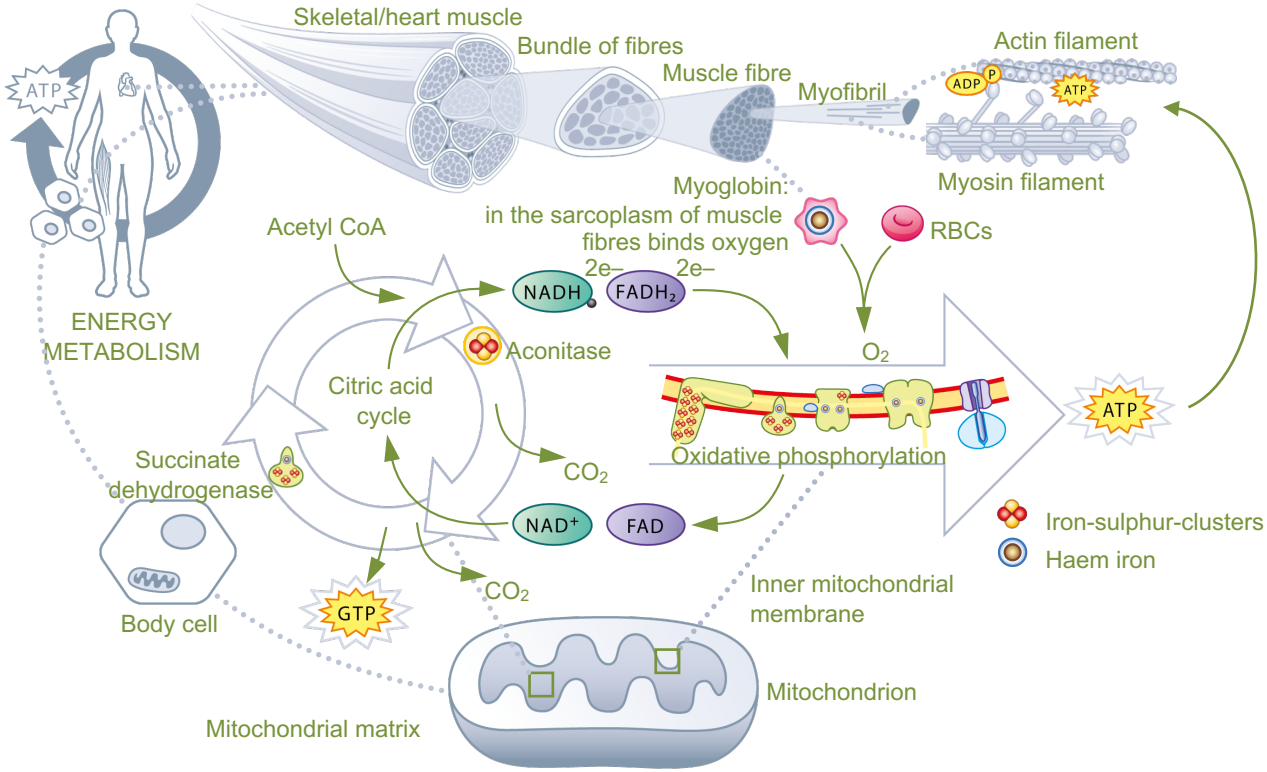
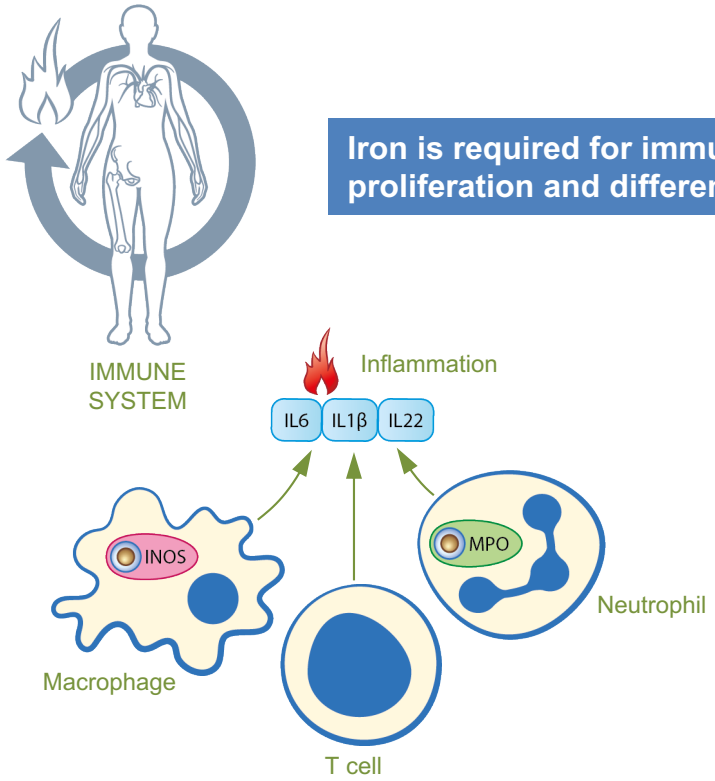
Energy metabolism and muscle function



ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme A; FAD, flavin adenine dinucleotide; GTP, guanosine triphosphate; NAD/NADH, nicotinamide adenine dinucleotide/+hydrogen

Musallam KM, Taher AT. *Curr Med Res Opin* 2018;34:81–93

Immunity



Iron is required for immune cell growth, proliferation and differentiation

Immune cells require iron as a cofactor in the production of enzymes, such as MPO and iNOS, for eradication of intracellular pathogens

IL, interleukin; iNOS, nitric oxide synthase; MPO, myeloperoxidase

Musallam KM, Taher AT. *Curr Med Res Opin* 2018;34:81–93

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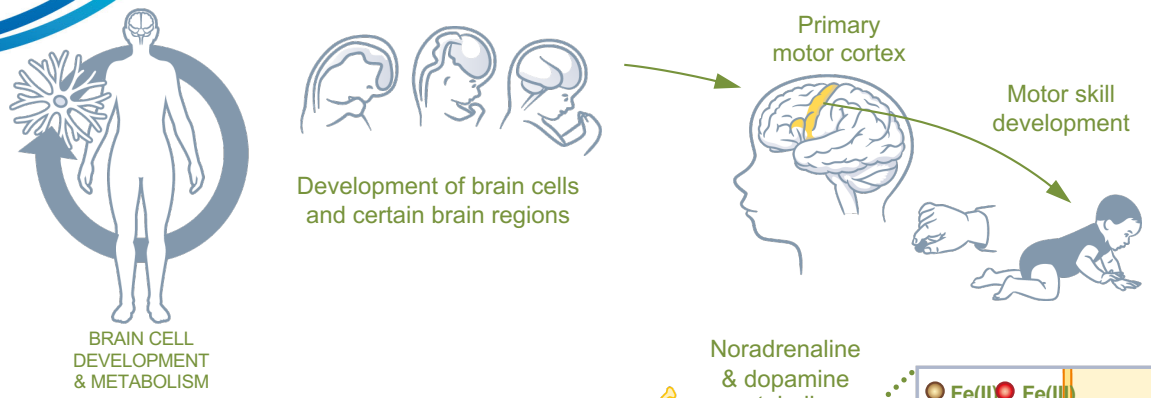
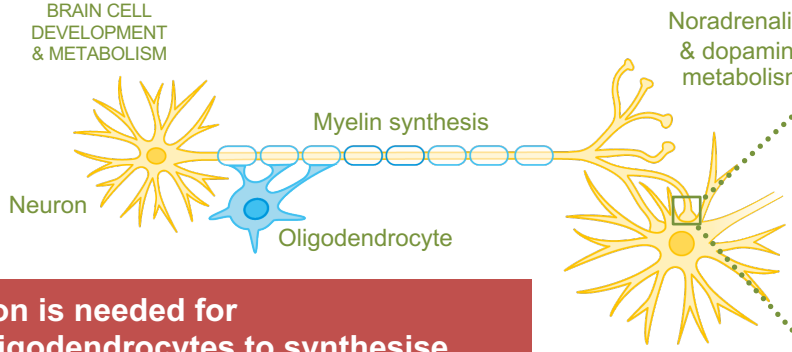
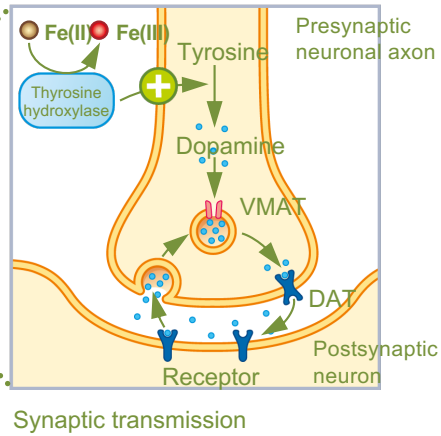
Development and function of brain cells



Iron is needed for proper neurogenesis and development



Iron is needed for oligodendrocytes to synthesise fatty acids and cholesterol for myelin



Iron is also essential for neurotransmitter synthesis, including tryptophan hydroxylase used to produce serotonin, and tyrosine hydroxylase used to synthesise norepinephrine and dopamine

DAT, dopamine transporter; VMAT, vesicular monoamine transporter

Radlowski EC, Johnson RW. *Front Hum Neurosci* 2013;7:585

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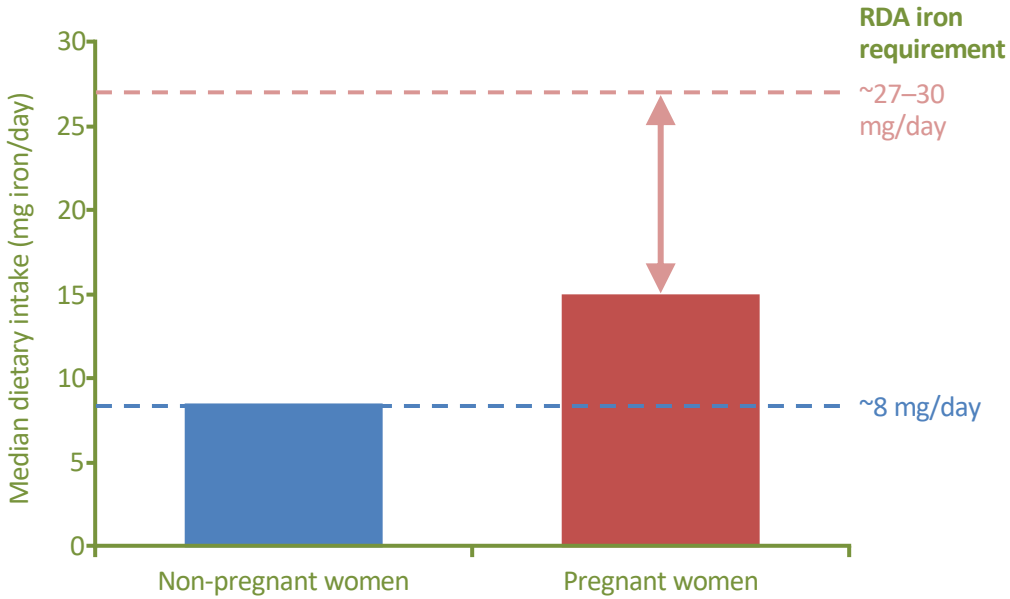
The high iron demands during pregnancy may not be met by dietary intake

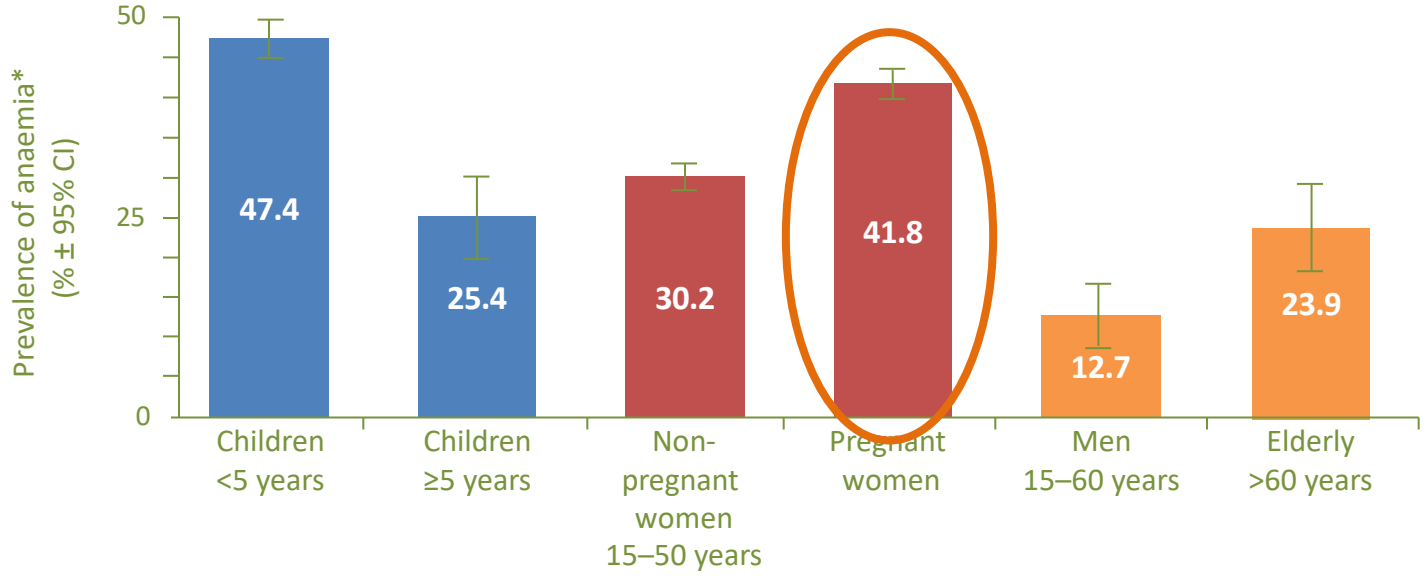
- **Only a small proportion of dietary iron (~1–2 mg) is absorbed in healthy individuals**



RDA, recommended daily allowance

Friedrisch JR, Friedrisch BK. *Biochem Insights* 2017;10:1–8; Scholl TO. *Nutr Rev* 2011;69:S23–S29; Khalafallah AA, Dennis AE. *J Pregnancy* 2012:2012:630519; Achebe MM, Gafter-Gvili A. *Blood* 2017;129:940–9

Worldwide, >40% of pregnant women are anaemic



*Including industrialised countries: children (6–59.9 months) Hb <11 g/dL; children (5–11.99 years) Hb <11.5 g/dL; children (12–14.99 years) Hb <12.0 g/dL; pregnant women Hb <11.0 g/dL;
non-pregnant women Hb <12.0 g/dL; men Hb <13.0 g/dL
CI, confidence interval
Data source: WHO. Worldwide prevalence of anaemia,1993–2005. 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf

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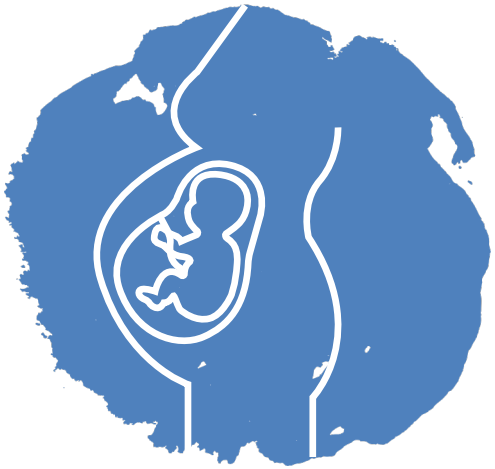
Maternal effects of anaemia



- Increased maternal mortality[1,2]
- Fatigue and postnatal depression[1,3–5]
- Cardiac compromise during labour[1,6–8]
- Increased risk of postpartum haemorrhage[9–12]
- Greater risk of puerperal sepsis and poor wound healing[13–14]

1. Breymann C. *Hematology Am Soc Hematol Educ Program* 2017;2017:152–9; 2. Daru J *et al. Lancet Glob Health* 2018;6:e548–e554; 3. Corwin EJ *et al. J Nutr* 2003;133:4139–42; 4. Van Wyck D *et al*. *Obstet Gynecol* 2007;110:267–78; 5. Eckerdal P *et al. PLoS One* 2016;11:e0144274; 6. Viteri FE. *SCN News* 1994;11:14–8;
7. Villar J *et al*. *J Nutr* 2003;133:S1606S–S1625; 8. Reveiz L *et al*. *Cochrane Database Syst Rev* 2011;10:CD003094; 9. A2Z /ACCESS/FANTA. Maternal Anemia: A Preventable Killer (2006); 10. Wang X *et al. J Cent South Univ (Med Sci)* 2014;39:151–6; 11. Nyfløt LT *et al. BMC Pregnancy & Childbirth* 2017;17:17; 12. Briley A *et al. BJOG* 2014;121:876–88; 13. Acosta CD *et al. PLoS Med* 2014;11:e1001672; 14. Acosta CD *et al. BJOG* 2012;119:474–83; 15. Chen Y *et al. Arch Gynecol Obstet* 2017;296:355–61

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Risk factors for PPH

LOW RISK

- Singleton
- Fewer than four previous deliveries
- Unscarred uterus
- Absence of PPH history

MEDIUM RISK

- Previous caesarean section or uterine surgery
- More than four previous deliveries
- Multiple gestation
- Large uterine fibroids
- Chorioamnionitis
- Magnesium sulfate use
- Prolonged use of oxytocin

HIGH RISK

- Placenta previa, accreta, increta, percreta
- Placental abruption
- Ante-, intra-partum bleeding
- History of PPH
- Known coagulation defect
- Haematocrit <30%

However, most cases display no risk factors

PPH, postpartum haemorrhage

1. From ACOG Practice Bulletin #183. *Obstet Gynecol* 2017;130:e168–e186

Postpartum haemorrhage

A UK large prospective observational study

- 60% of women with Hb <85 g/l sustained PPH
- 25% progressed to severe PPH

(Briley *et al*, **2014**).

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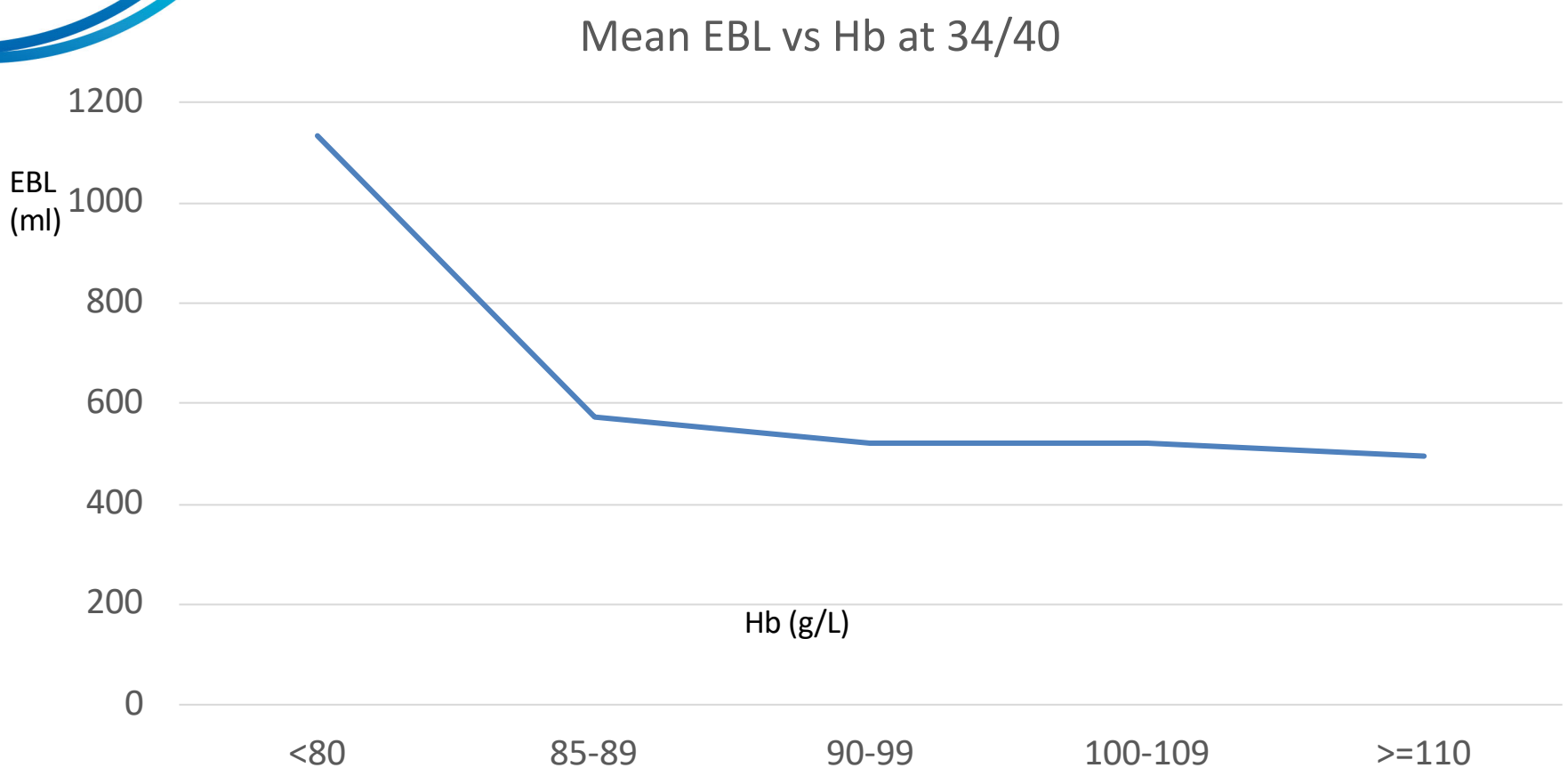
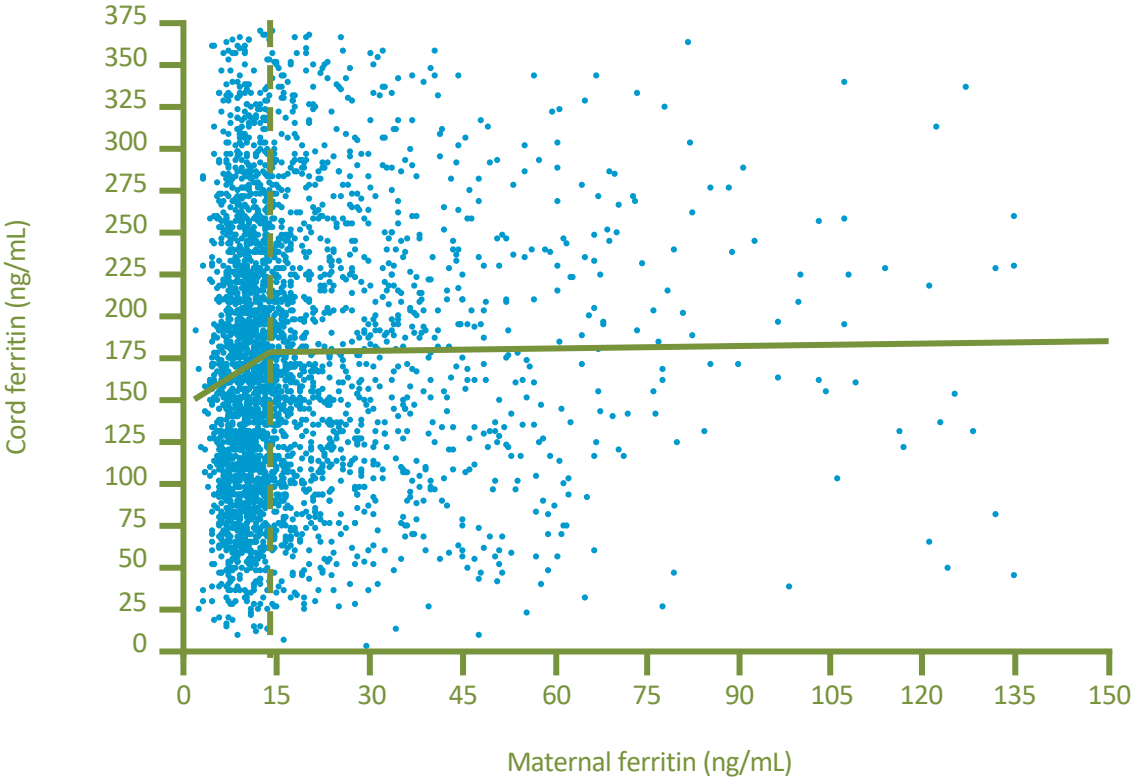
Oxford Data n=6322



Iron delivery to the fetus

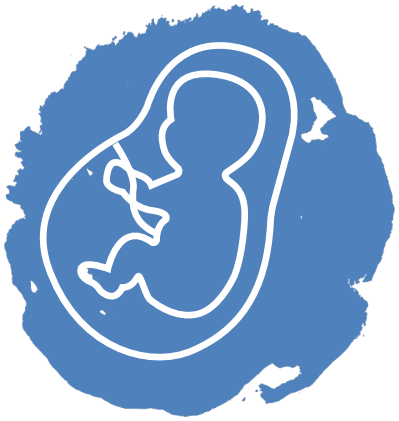
- Preferential delivery of iron to the fetus
- transferrin receptors on trophoblastic membranes
- Maternal iron bound to transferrin is endocytosed
- Transported to the fetus as apotransferrin
- Transfer of iron predominantly last 4 weeks
- 2/3rd fetal iron in fetal haemoglobin

When is fetal iron status compromised with maternal anemia?



Shao *et al. J Nutr* 2012;142:2004–9

Fetal effects of anaemia



- Systematic reviews of LMICs show higher rates of perinatal/neonatal mortality[1]
  - Increased risk of:
    - Premature delivery
    - Low birth weight
- Potential risk to developing brain structures, neurotransmitter systems and myelination[2]
- Observational studies show lower Apgar scores,[3,4] impaired neonatal cognition[5]

LMIC, low- and middle-income countries

1. Rahman MM *et al. Am J Clin Nutr* 2016;103:495–504; 2. Georgieff MK. *Biochem Soc Trans* 2008;36(Pt 6):1267–71; 3. Çakmak BD *et al. Turk J Obstet Gynecol* 2018;15:165–70;
4. Anjanappa B *et al. Int J Reprod Contracept Obstet Gynecol* 2015;4:1335–8; 5. Grantham-McGregor S, Ani C. *J Nutr* 2001;131:S649–S666

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Diagnosis of iron deficiency in pregnancy

- Hb levels
- Red cell indices
- Serum ferritin – cut off in pregnancy of 30 µg/L
- Transferrin saturation

→ Trial of iron therapy

Pavord S *et al. Br J Haematol* 2012;156:588–600

Diagnosis of iron deficiency in pregnancy

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Trial of Iron therapy!

Pavord S *et al. Br J Haematol* 2012;156:588–600

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Indications for empirical iron treatment and/or serum ferritin testing

Women with anaemia where testing serum ferritin is necessary prior to iron supplementation to exclude an iron loading state

- Known haemoglobinopathy
- Prior to parenteral iron replacement

Women without anaemia with high risk of iron depletion for empirical iron treatment with/without serum ferritin testing

- Previous anaemia
- Multiparity ≥P3
- Twin or higher order multiple pregnancy
- Interpregnancy interval <1 year
- Women who have poor dietary habits
- Those following a vegetarian/vegan diet
- Pregnant teenagers
- Recent history of clinically significant bleeding

Women without anaemia where serum ferritin may be necessary to ensure adequate iron reserves for delivery

- High risk of bleeding during pregnancy or at birth
- Women declining blood products
- Women for whom providing compatible blood is challenging eg due to red cell antibodies

Adapted from Pavord S *et al. Br J Haematol* 2012;156:588–600

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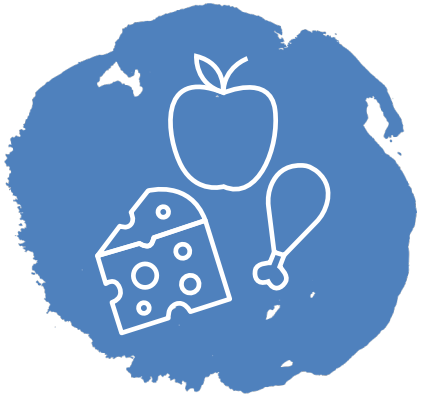
Treatment of iron deficiency



Dietary advice

Oral iron supplements

Intramuscular iron injections

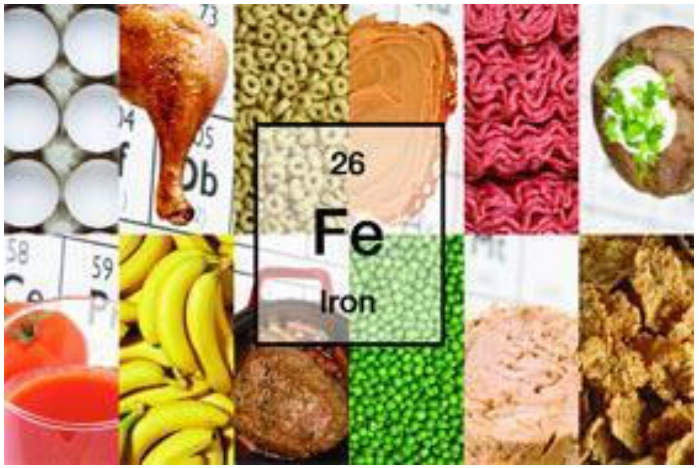
Intravenous iron

Transfusion – not unless there is severe anaemia with imminent cardiac compromise

Dietary iron

- 10 – 20 mg in diet
- 10 – 20% is absorbed
- The bioavailability of iron depends on its chemical form:

  haem iron in blood, muscle meat includes fish, chicken
  - Haem iron better absorbed



Factors inhibiting absorption	Factors enhancing absorption
Foods rich in calcium	Heme iron
Tannins in tea	Ferrous iron
Phytates in cereals	Ascorbic acid

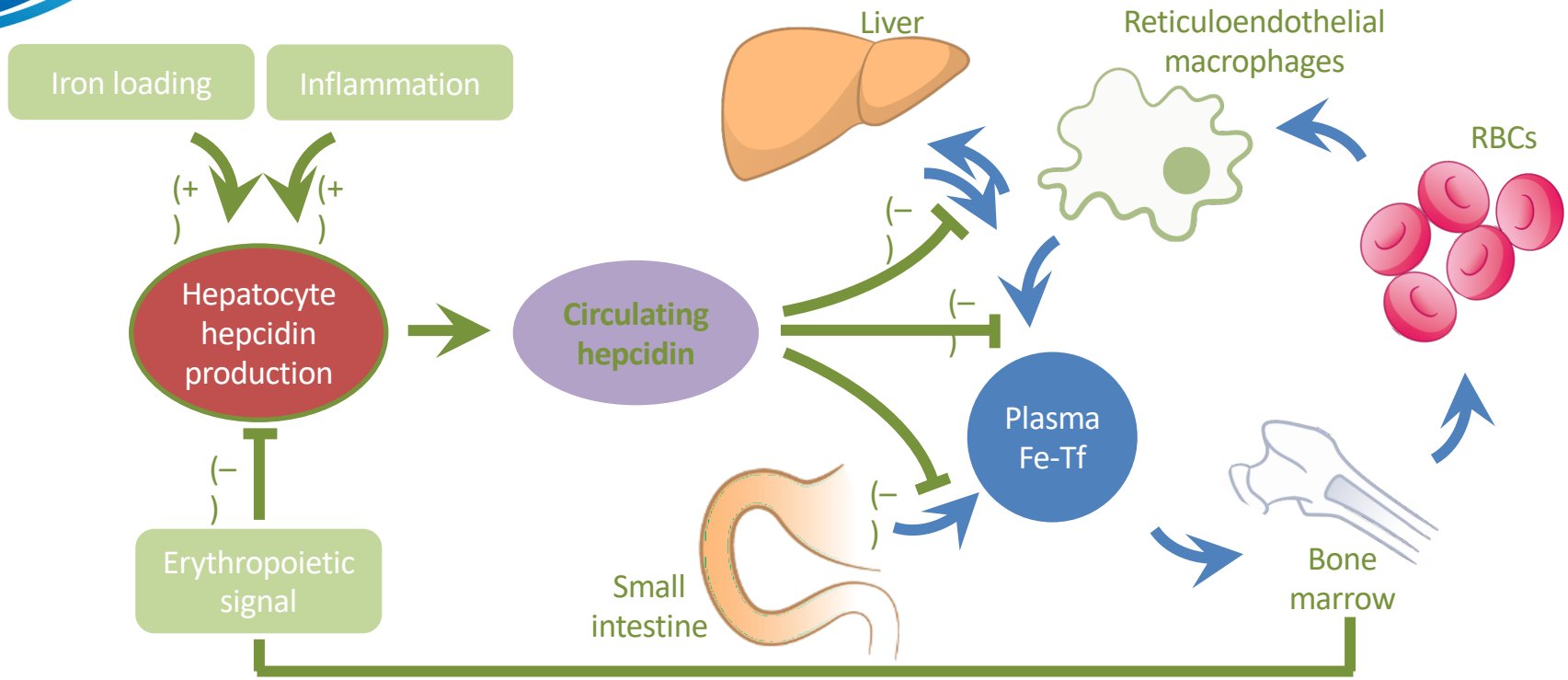
Oral preparations

Epigastric pain and nausea are dose related
Constipation/ diarrhoea possibly not dose related

Ferrous iron salt	Amount	Elemental iron
Fumarate	200 mg	65 mg
Gluconate	300 mg	35 mg
Sulphate (dried)	200 mg	65 mg

Only 7mg iron /10mls

Hepcidin



Fe-Tf, iron-transferrin complex

Figure adapted from Young B, Zaritsky J. *Clin J Am Soc Nephrol* 2009;4:1384–7

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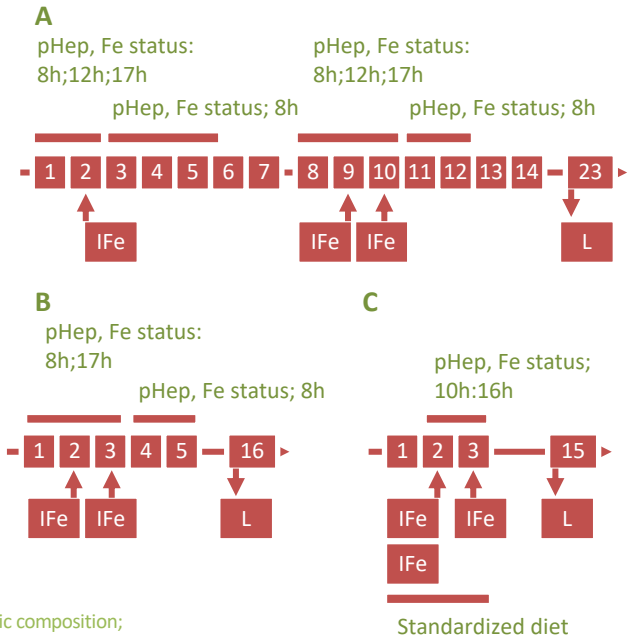
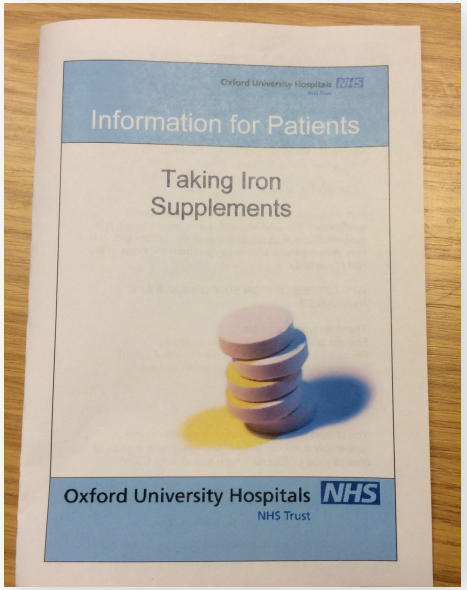
Considerations for iron treatment

What dosing regime?

Study of oral iron absorption[1]



Information for patients



IFe, labeled iron supplement administration; L, determination of isotopic composition; pHep, plasma hepcidin; 1. Moretti D *et al. Blood 2015;*126:1981–9

The route: oral iron

Benefits	Limitations
• Inexpensive • Can be used throughout a woman's life cycle (including all trimesters of pregnancy) • Easily accessible • Allows for future self-management	• Limited absorption • Slower Hb response • GI side effects • Low compliance leads to inadequate treatment response

GI, gastrointestinal

Cappellini MD *et al. Am J Hematol* 2017;92:1068–78; Mirza FG *et al. Expert Rev Hematol* 2018;11:727–36

The route: IV iron

IV iron is recommended in cases when:	• Oral iron is ineffective or cannot be used • Moderate-to-large amounts of iron are required • Need for rapid repletion
Advantages of IV iron over oral iron preparations	• Fast repletion of iron stores even in severe ID → fast haematological response • Effective in patients with inflammatory disease • Fewer GI side effects compared with oral iron preparations • Good control over compliance

Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with IV iron should be confined to the second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the fetus

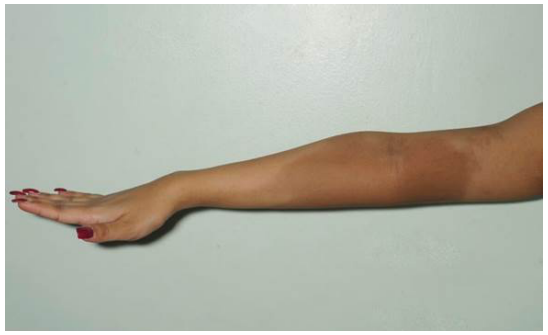
IV, intravenous

Geisser P, Burckhardt S. *Pharmaceutics* 2011;3:12–33; Bailie GR *et al. Arzneimittelforschung* 2011;61:267–75

The route: IV iron

Points to consider

- Risk of hypersensitivity reactions
- Higher frequency observed with high-molecular iron dextrans vs IS and ferric gluconate
- Extravasation needs to be avoided (skin discolouration)

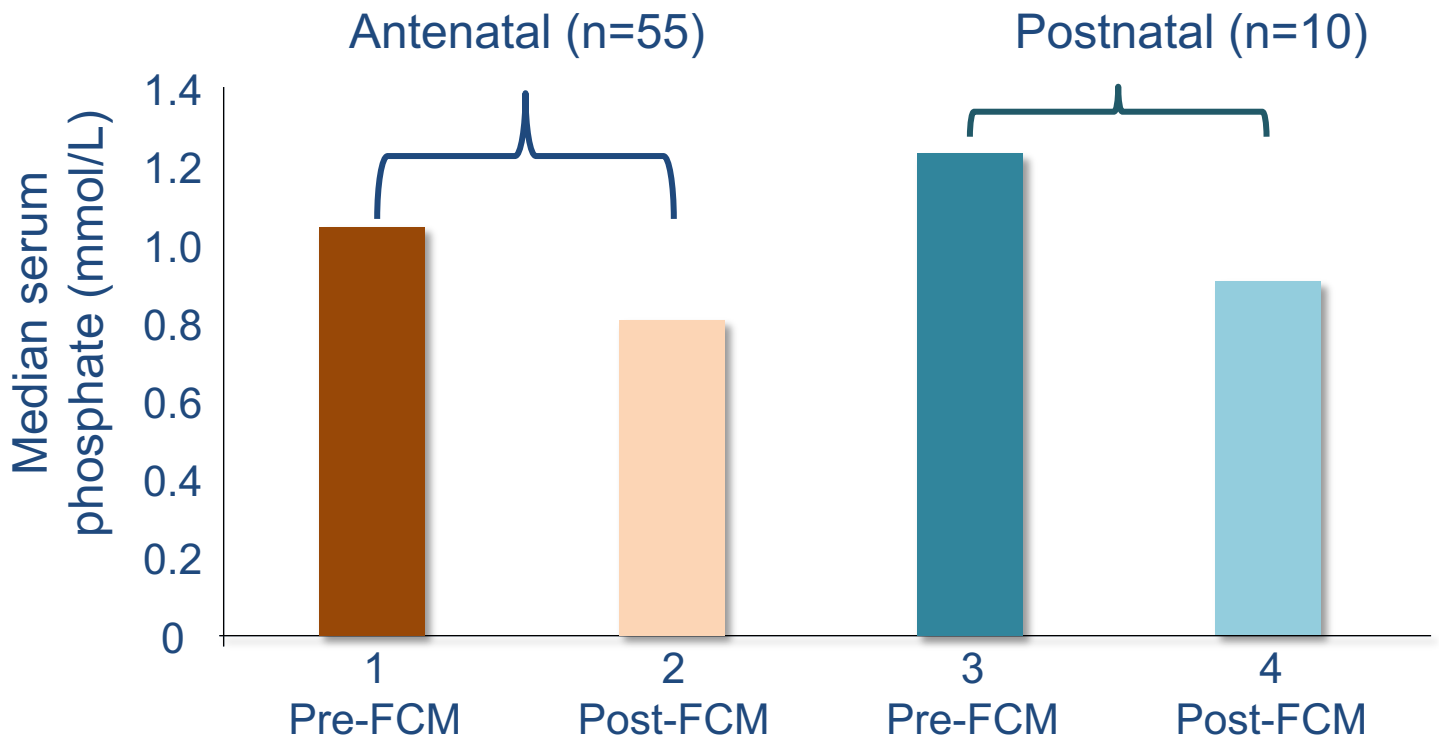


IS, iron sucrose

Geisser P, Burckhardt S. *Pharmaceutics* 2011;3:12–33; Bailie GR *et al. Arzneimittelforschung* 2011;61:267–75

Phosphate levels

- 65 women. Mean age: 32 years
- Median phosphate level: 1.07 mmol/L at baseline (IQR1.3)
- Median phosphate level 0.82 mmol/L post FCM (IQR2.06)



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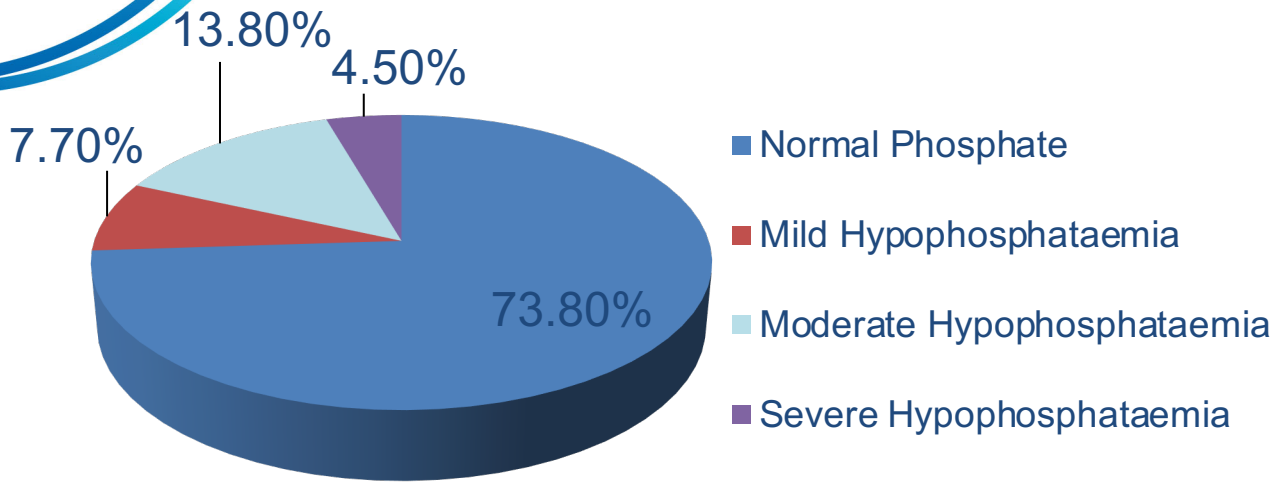
Prevalence of Hypophosphataemia at OUH following FCM administration



Prevalence of hypophosphataemia: 26.2%

Oxford local guidelines for treatment of low phosphate levels:

Moderate asymptomatic hypophosphataemia (0.41–0.60 mmol/l)	Moderate symptomatic hypophosphataemia (0.41–0.60 mmol/l)	Severe hypophosphataemia (<0.4 mmol/l)
Phosphate Sandoz Effervescent tablets Two tablets BD (16 mmol phosphate/tablet)	20 mmol phosphate as sodium glycerophosphate in 0.9% sodium chloride or 5% glucose over 6 hours (IV)	20 mmol phosphate as sodium glycerophosphate in 0.9% sodium chloride or 5% glucose over 6 hours (IV)

1. Kotechi A, et al. Poster presented ISH Conference 2016.

FCM: ferric carboxymaltose

Intravenous Iron

- Well tolerated
- Side effects very unusual
- Risk of significant anaphylaxis <1:1000

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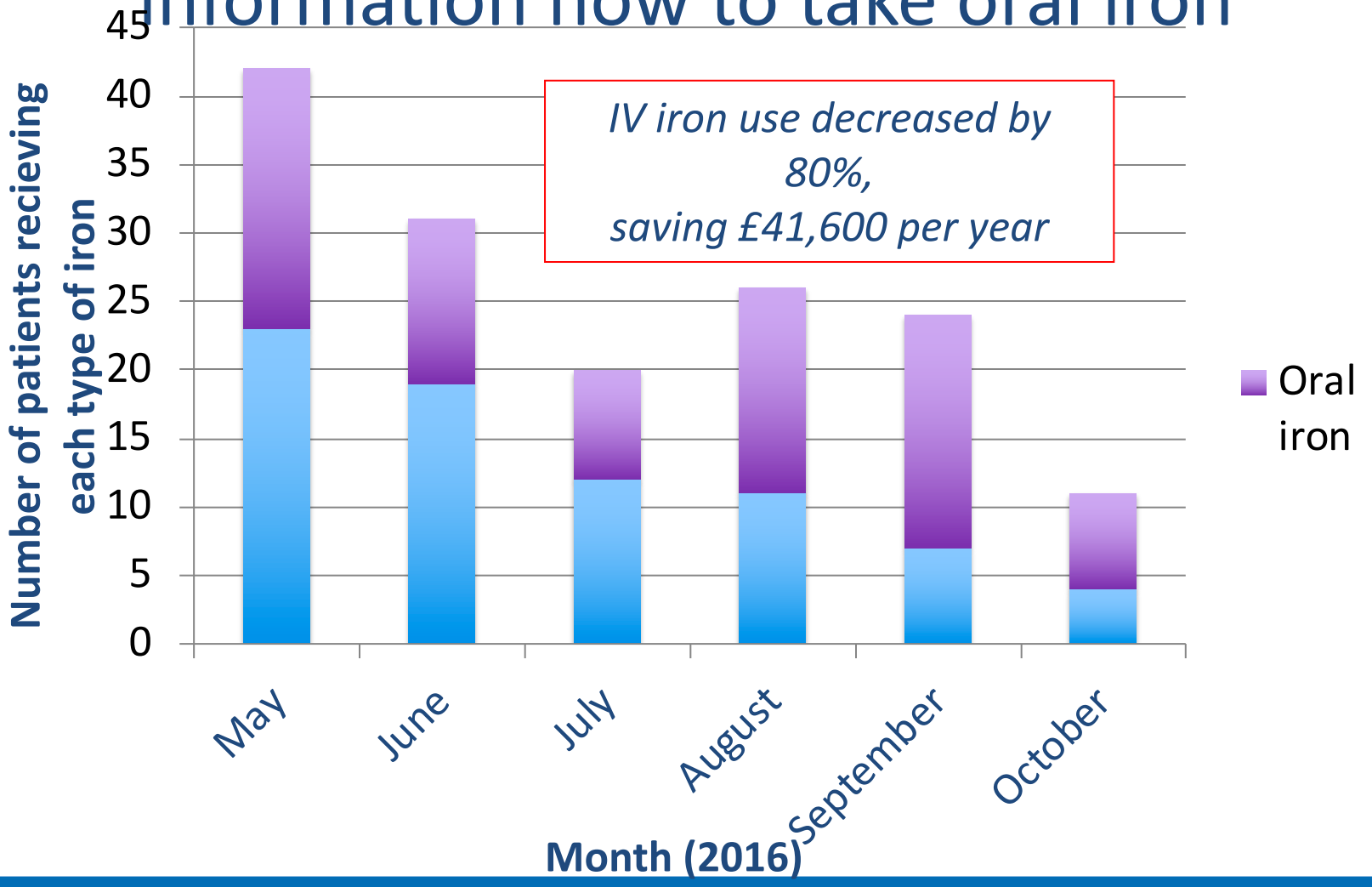
Reduction in iv iron use after giving information how to take oral iron



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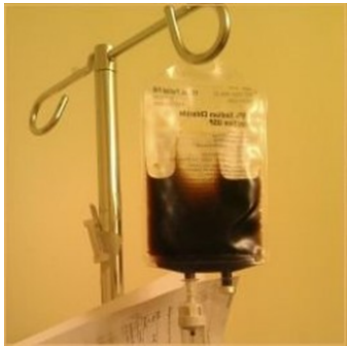
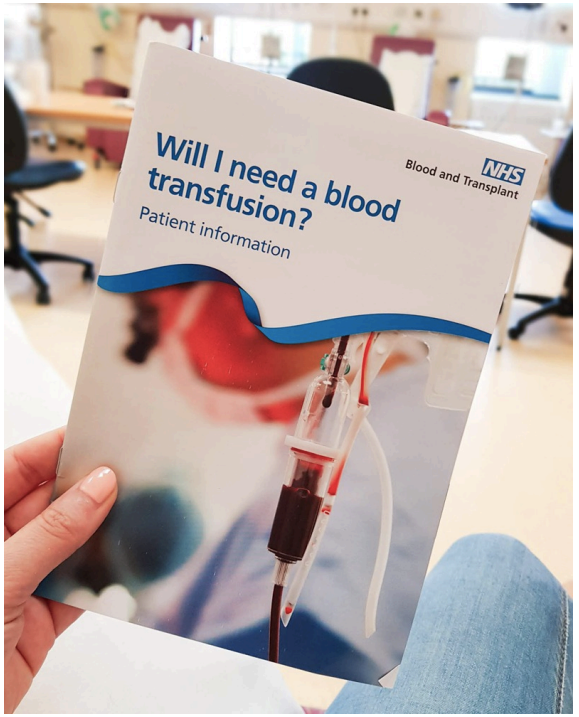
Blood transfusion



Postpartum women, not bleeding:

Transfusion is not indicated if Hb >70g/l, unless there is a significant risk of re-bleeding or cardiac compromise

Transfusion at Hb below <70 g/l should only be necessary if the patient is symptomatic



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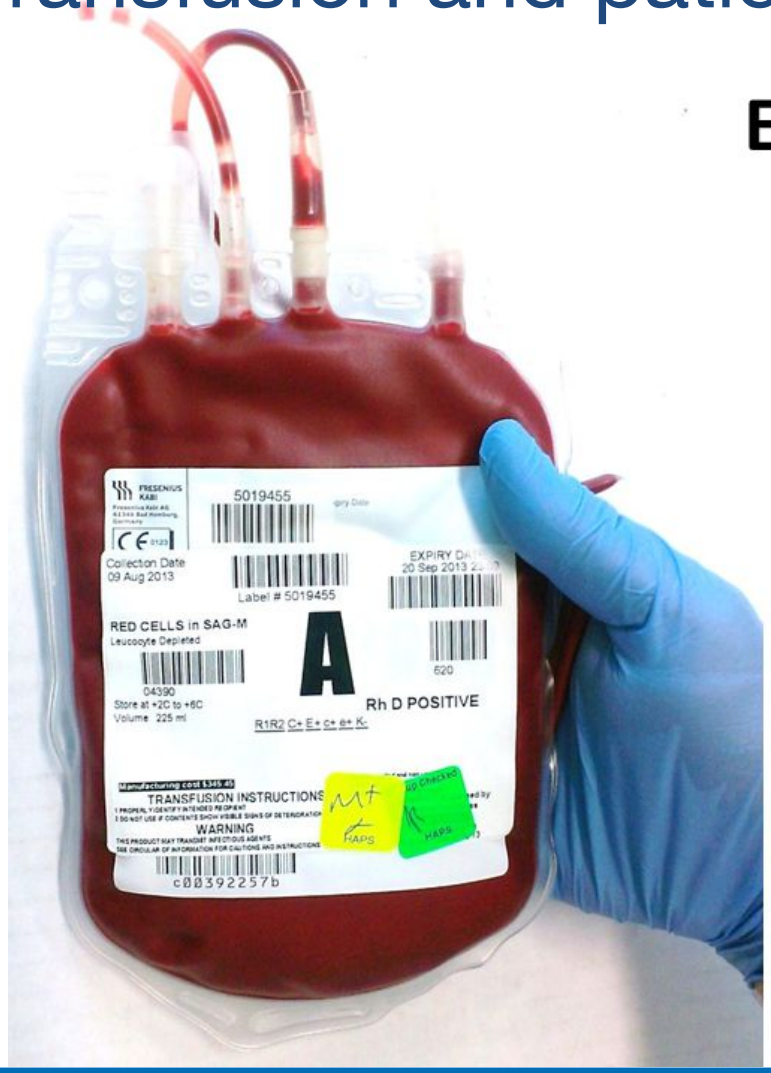
Transfusion and patient assessment



Every ONE matters

Transfuse **One** Unit

↓

Re-assess the patient

↓

Don't increase the RISKS

if

NO BENEFIT

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Treatment summary

Oral iron is the first-line treatment for ID/IDA

IV iron is the treatment of choice in women requiring rapid response or being intolerant to oral iron

- More rapid and more frequent Hb normalisation than with oral iron
- In contrast to oral iron, IV iron effectively repletes iron stores
- IV iron is well tolerated

Blood transfusion should be reserved for those with:

- Risk of further bleeding
- Imminent cardiac compromise
- Symptoms requiring immediate attention

Antenatal Anaemia at OUH

	n	Mean Hb g/L (range)	Median	No of pts Anaemic (Hb<110 booking, Hb< 105 2nd/3rd TM, Hb <100 PP)	% Anaemic of those tested
Booking	4886	128.7 (62- 174)	129	110	2.3
28/40	6313	115.2 (52- 149)	115	790	12.5
34/40	6322	115.6 (73- 156)	115	696	11.0
Pre-delivery	4232	121.4 (51-225)	122	278	6.4
Post-delivery	*3667*	*106.2 (52-180)*	*106*	*1189*	*32.4*

397 women (5.4%) received ferrinject

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Postpartum anaemia

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2017)

ORIGINAL PAPER

Vox Sanguinis published by John Wiley & Sons Ltd on behalf of International Society of Blood Transfusion
DOI: 10.1111/vox.12477

Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial

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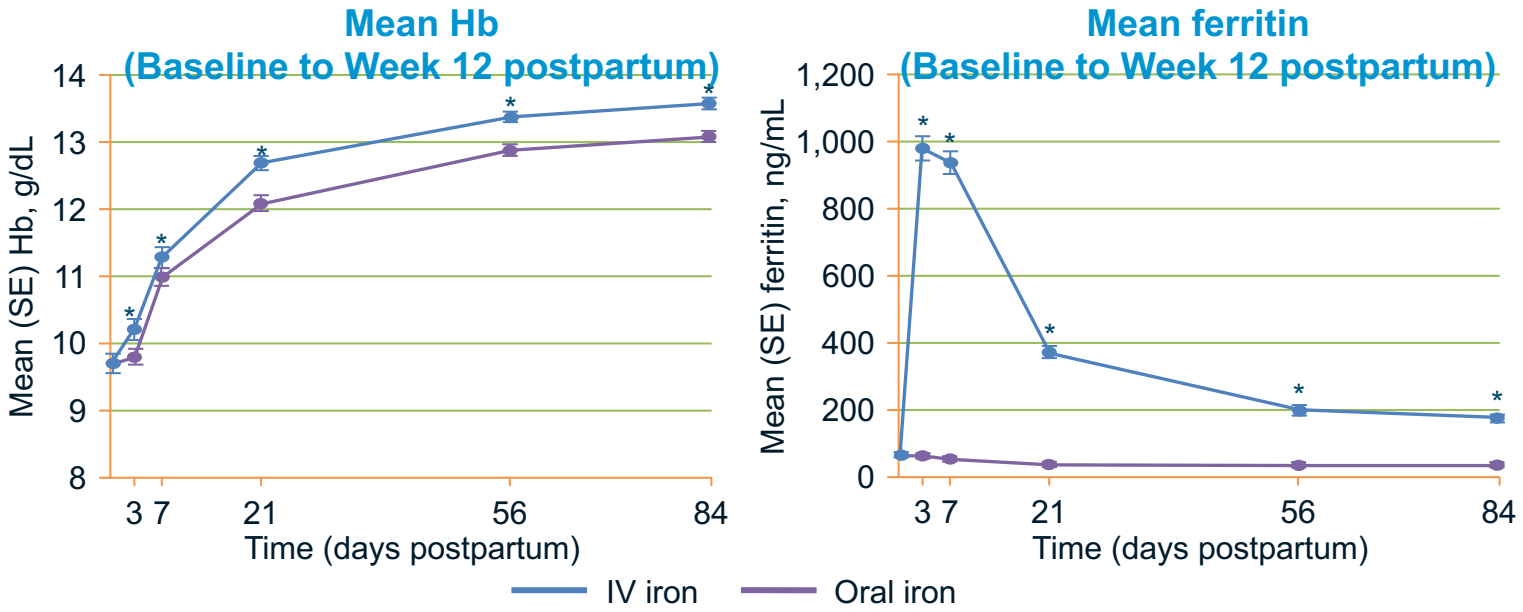
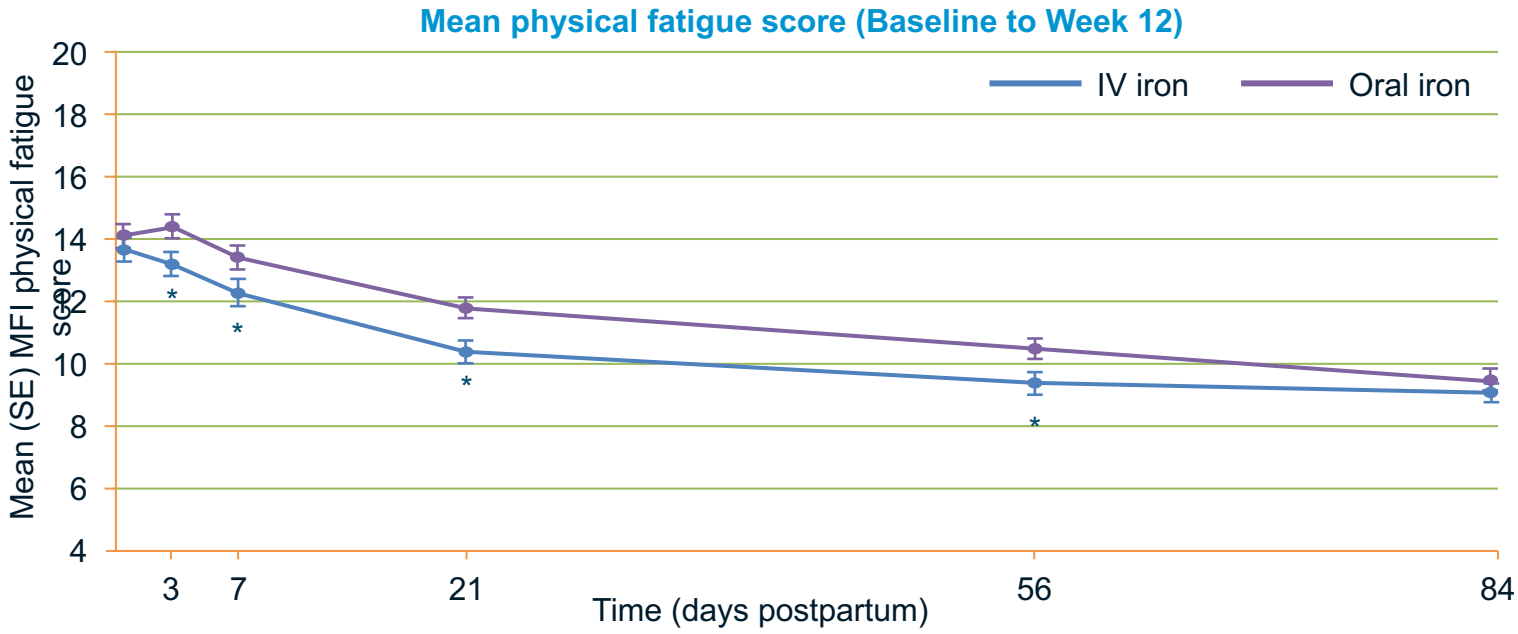
Hb response


Mean Hb
(Baseline to Week 12 postpartum)
Mean (SE) Hb, g/dL
14
13
12
11
10
9
8
3 7
21
56
84
Time (days postpartum)
Mean ferritin
(Baseline to Week 12 postpartum)
Mean (SE) ferritin, ng/mL
1,200
1,000
800
600
400
200
0
3 7
21
56
84
Time (days postpartum)
IV iron
Oral iron

Postpartum fatigue



Prevention of iron deficiency

- Why not supplement all?

Potential hazards of iron therapy

- Risk of Fe overload in women with :
  - Fe loading states e.g. haemochromatosis
  - Repeat transfusions e.g. haemoglobinopathies
- Risks of high Hb
  - Large observational study of 54,382 pregnancies
  - Higher rates of perinatal death, low birth weights and preterm delivery in women with high (Hb >13.2g/dl) compared to intermediate Hb levels, at 13-19 weeks gestation
  - A booking Hb of >14.5g/dl was associated with a 42% risk of subsequent hypertension

Murphy, J.F., O'Riordan, J., Newcombe, R.G., Coles, E.C., Pearson, J.F. (1986) Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. The Lancet 327, 992-995.

Cochrane review

- 49 trials, involving 23,200 pregnant women
- Oral iron supplementation was associated with increased maternal haemoglobin in the antenatal and postnatal period
- And women taking supplements less likely to be iron deficient at term (RR 30-50%)
- no evidence to suggest a significant reduction in maternal and neonatal adverse clinical outcome

Problems

- High cost
- Logistical difficulties
- Inadequate counselling
- Poor compliance
- Potential risk of accidental overdose by children in the home

Concluding messages

- IDA is common in pregnancy
- Has potentially serious consequences for mother and baby
- Early detection is vital to allow effective management
- to reduce the risk of pregnancy complications and need for blood transfusion