

CHAPTER 1

Iron Deficiency Anaemia

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OVERVIEW

- Iron deficiency is the commonest cause of anaemia worldwide
- Iron deficiency is usually easily diagnosed from the red cell indices
- A drop in haemoglobin is generally a late feature of iron deficiency
- The serum ferritin is a reliable means of confirming the diagnosis but may be falsely normal or even elevated as a reactive phenomenon as ferritin is an acute phase protein
- Iron deficiency is not a diagnosis in itself and in males and postmenopausal women blood loss from the gastrointestinal tract must be excluded
- Oral iron is preferred for iron replacement therapy, but occasionally parenteral iron is required

Box 1.1 Risk factors for development of iron deficiency

- **Age:** infants (especially if there is a history of prematurity); adolescents; postmenopausal women; elderly people
- **Sex:** increased risk in women
- **Reproduction:** menorrhagia
- **Renal:** haematuria (rarer cause)
- **Gastrointestinal tract:** appetite or weight changes; changes in bowel habit; bleeding from rectum/melaena; gastric or bowel surgery
- **Drug history:** especially aspirin and non-steroidal anti-inflammatories
- **Social history:** diet, especially vegetarians
- **Physiological:** pregnancy; infancy; adolescence; breastfeeding; age of weaning

Iron deficiency is the commonest cause of anaemia worldwide and is frequently seen in general practice. Iron deficiency anaemia is caused by defective synthesis of haemoglobin, resulting in red cells that are smaller than normal (microcytic) and contain reduced amounts of haemoglobin (hypochromic).

Iron metabolism

Iron has a pivotal role in many metabolic processes, and the average adult contains 3–5 g of iron, of which two-thirds is in the oxygen-carrying molecule haemoglobin.

A normal Western diet provides about 15 mg of iron daily, of which 5–10% is absorbed (~1 mg), principally in the duodenum and upper jejunum, where the acidic conditions help the absorption of iron in the ferrous form. Absorption is helped by the presence of other reducing substances, such as hydrochloric acid and ascorbic acid. The body has the capacity to increase its iron absorption in the face of increased demand, for example, in pregnancy, lactation, growth spurts and iron deficiency (Box 1.1).

Once absorbed from the bowel, iron is transported across the mucosal cell to the blood, where it is carried by the protein transferrin to developing red cells in the bone marrow. Iron stores comprise ferritin, a labile and readily accessible source of iron and haemosiderin, an insoluble form found predominantly in macrophages.

About 1 mg of iron a day is shed from the body in urine, faeces, sweat

and cells shed from the skin and gastrointestinal tract. Menstrual losses of an additional 20 mg per month and the increased requirements of pregnancy (500–1000 mg) contribute to the higher incidence of iron deficiency in women of reproductive age (Table 1.1, Box 1.2).

Clinical features of iron deficiency

The symptoms accompanying iron deficiency depend on how rapidly the anaemia develops. In cases of chronic, slow blood loss, the body adapts to the increasing anaemia and patients can often tolerate extremely low concentrations of haemoglobin, for example, <7.0 g/dL, with remarkably few symptoms. Most patients complain of increasing lethargy and dyspnoea. More unusual symptoms are headaches, tinnitus and taste disturbance.

Table 1.1 Daily dietary iron requirements

	Amount (mg)
Male	1
Adolescence	2–3
Female (reproductive age)	2–3
Pregnancy	3–4
Infancy	1
Maximum bioavailability from normal diet	~4

Box 1.2 Causes of iron deficiency anaemia

Reproductive system

- Menorrhagia

Gastrointestinal tract*Bleeding*

- Oesophagitis
- Oesophageal varices
- Hiatus hernia (ulcerated)
- Peptic ulcer
- Inflammatory bowel disease
- Haemorrhoids (rarely)
- Carcinoma: stomach, colorectal
- Angiodysplasia
- Hereditary haemorrhagic telangiectasia (rare)

Malabsorption

- Coeliac disease
- Atrophic gastritis (also may result from iron deficiency)

Physiological

- Growth spurts (especially in premature infants)
- Pregnancy

Dietary

- Vegans
- Elderly
- Other
- Patients with chronic renal failure undergoing haemodialysis and receiving erythropoietin

Worldwide commonest cause of iron deficiency is hookworm infection

On examination, several skin, nail and other epithelial changes may be seen in chronic iron deficiency. Atrophy of the skin occurs in about a third of patients and (rarely nowadays) nail changes such as koilonychia (spoon-shaped nails; Fig. 1.1) may result in brittle, flattened nails. Patients may also complain of angular stomatitis, in which painful cracks appear at the angle of the mouth, sometimes accompanied by glossitis. Although uncommon, oesophageal and pharyngeal webs can be a feature of iron deficiency anaemia (consider this in middle aged women presenting with dysphagia). These changes are believed



Figure 1.1 Nail changes in iron deficiency anaemia (koilonychia).

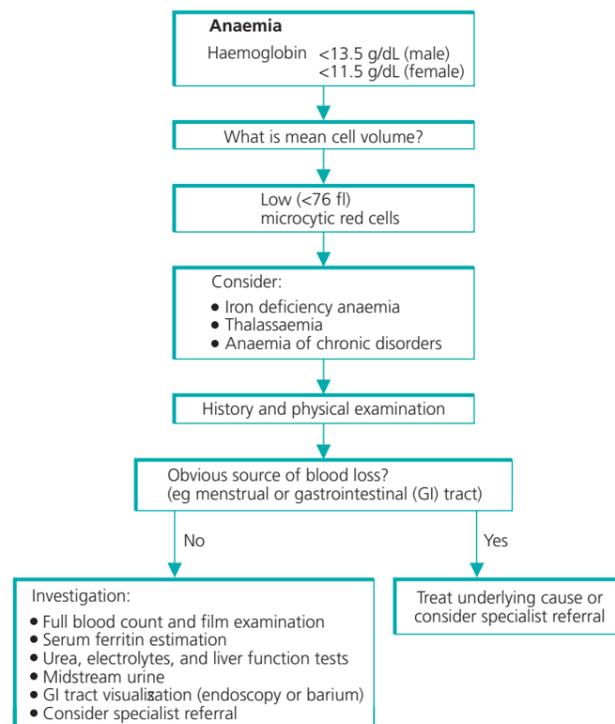


Figure 1.2 Diagnosis and investigation of iron deficiency anaemia.

to be due to a reduction in the iron-containing enzymes in the epithelium and gastrointestinal tract. Few of these epithelial changes are seen in modern practice, and they are of limited diagnostic value.

Tachycardia and cardiac failure may occur with severe anaemia irrespective of cause and, in such cases, prompt remedial action should be taken.

When iron deficiency is confirmed, a full clinical history, including leading questions on possible gastrointestinal blood loss or malabsorption (as in, for example, coeliac disease), should be obtained. Menstrual losses should be assessed and the importance of dietary factors and regular blood donation should not be overlooked (Fig. 1.2).

Diet alone is seldom the sole cause of iron deficiency anaemia in the UK except when it prevents an adequate response to a physiological challenge, as in pregnancy, for example.

Laboratory investigations

A full blood count and film should be assessed (Box 1.3). These will confirm the anaemia; recognizing the indices of iron deficiency is usually straightforward (reduced haemoglobin concentration, reduced mean cell volume, reduced mean cell haemoglobin, reduced mean cell haemoglobin concentration) (Table 1.2). Some modern analysers will determine the percentage of hypochromic red cells, which may be high before the anaemia develops (it is worth noting that a reduction in haemoglobin concentration is a late feature of iron deficiency). The blood film shows microcytic hypochromic red cells (Fig. 1.3). Hypochromic anaemia occurs in other disorders, such as anaemia of chronic disorders and sideroblastic anaemias,

Box 1.3 Investigations in iron deficiency anaemia

- Full clinical history and physical examination
- Full blood count and blood film examination
- Haematinic assays (serum ferritin, vitamin B₁₂, folate)
- Note serum iron and TIBC now obsolete
- Percentage of hypochromic red cells and soluble transferrin receptor assay (if available)
- Urea and electrolytes, liver function tests
- Fibreoptic and/or barium studies of the gastrointestinal tract
- Pelvic ultrasound (female patients, if indicated)

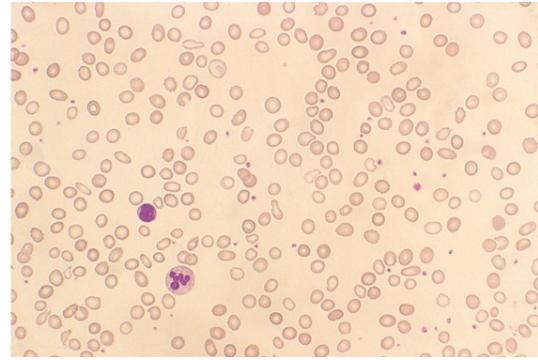


Figure 1.3 Blood film showing changes of iron deficiency anaemia.

and in globin synthesis disorders, such as thalassaemia (Table 1.3). To help to differentiate the type, further haematinic assays may be necessary. Historically, serum iron and total iron binding capacity (TIBC) were used in the diagnosis of iron deficiency anaemia, but because of the wide diurnal variation seen in iron levels and the lack of sensitivity, these assays are seldom used today. Difficulties in diagnosis arise when more than one type of anaemia is present, for example, iron deficiency and folate deficiency in malabsorption, in a population where thalassaemia is present, or in pregnancy, when the interpretation of red cell indices may be difficult.

Haematinic assays will demonstrate reduced serum ferritin concentration in straightforward iron deficiency. As an acute phase protein, however, the serum ferritin concentration may be normal or even raised in inflammatory or malignant disease.

A prime example of this is found in rheumatoid disease, in which active disease may result in a spuriously raised serum ferritin concentration masking an underlying iron deficiency caused by gastrointestinal bleeding after non-steroidal analgesic treatment. There may also be confusion in liver disease, as the liver contains stores of ferritin that are released after hepatocellular damage, leading to raised serum ferritin concentrations. In cases where ferritin estimation is likely to be misleading, the soluble transferrin receptor (sTfR) assay may aid the diagnosis.

Transferrin receptors are found on the surface of red cells in greater numbers in iron deficiency; a proportion of receptors is shed into the plasma and can be measured using commercial kits. Unlike serum ferritin, the level of sTfR does not rise in inflammatory disorders, and

Table 1.2 Diagnosis of iron deficiency anaemia

Reduced haemoglobin	Men <13.5 g/dl, women <11.5 g/dl
Reduced MCV	<76 fl (76–95 fl)
Reduced MCH	29.5 ± 2.5 pg (27.0–32.0 pg)
Reduced MCHC	32.5 ± 2.5 g/dl (32.0–36.0 g/dl)
Blood film	Microcytic hypochromic red cells with pencil cells and target cells
Reduced serum ferritin*	Men <10 µg/L, women (postmenopausal) <10 µg/L (premenopausal) <5 µg/L
Elevated % hypochromic red cells (>2%)	
Elevated soluble transferrin receptor level	

*Check with local laboratory for reference ranges. Note normal values in parentheses
MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume

Table 1.3 Characteristics of anaemia associated with other disorders

	Iron deficiency	Chronic disorders	Thalassaemia trait (α or β)	Sideroblastic anaemia
Degree of anaemia	Any	Seldom <9.0 g/dl	Mild	Any
MCV	↓	N or ↓	↓↓	N or ↓ or ↑
Serum ferritin	↓	N or ↑	N	↑
sTfR	↑	N	↑	N
Marrow iron	Absent	Present	Present	Present

MCV, mean corpuscular volume; N, normal; sTfR, soluble transferrin receptor assay

hence can help to differentiate between anaemia due to inflammation and iron deficiency.

Diagnostic bone marrow sampling is seldom performed in simple iron deficiency, but, if the diagnosis is in doubt, a marrow aspirate may be carried out to demonstrate absent bone marrow stores.

When iron deficiency has been diagnosed, the underlying cause should be investigated and treated. Often the history will indicate the likely source of bleeding, for example, menstrual blood loss or gastrointestinal bleeding. If there is no obvious cause, further investigation generally depends on the age and sex of the patient. In male patients and postmenopausal women, possible gastrointestinal blood loss is investigated by visualization of the gastrointestinal tract (endoscopic or barium studies). Faecal occult blood tests are of no value in the investigation of iron deficiency.

Management

Effective management of iron deficiency relies on (i) the appropriate management of the underlying cause (for example, gastrointestinal or menstrual blood loss) and (ii) iron replacement therapy.

Oral iron replacement therapy, with gradual replenishment of iron stores and restoration of haemoglobin, is the preferred treatment. Oral ferrous salts are the treatment of choice (ferric salts are less well absorbed) and usually take the form of ferrous sulphate 200 mg three times daily (providing $65 \text{ mg} \times 3 = 195 \text{ mg}$ elemental iron/day) (Fig. 1.4). Alternative preparations include ferrous gluconate and ferrous fumarate (Table 1.4). All three compounds, however, are associated with a high incidence of side effects, including nausea, constipation and diarrhoea. These side effects may be reduced by taking the tablets after meals, but even milder symptoms account for poor compliance with oral iron supplementation. It is worth noting that these lower gastrointestinal symptoms are not dose related. Modified release preparations have been developed to reduce side effects, but in practice prove expensive and often release the iron beyond the sites of optimal absorption.



Figure 1.4 Oral iron replacement therapy.

Table 1.4 Elemental iron content of various oral iron preparations

Preparation	Amount (mg)	Ferrous iron (mg)
Ferrous fumarate	200	65
Ferrous gluconate	300	35
Ferrous sulphate	300	60

Effective iron replacement therapy should result in a rise in haemoglobin concentration of around 0.1 g/dL per day (about 2 g/dL every 3 weeks), but this varies from patient to patient. Once the haemoglobin concentration is within the normal range, iron replacement should continue for 3 months to replenish the iron stores.

Failure to respond to oral iron therapy

The main reason for failure to respond to oral iron therapy is poor compliance. However, if the losses (for example, bleeding) exceed the amount of iron absorbed daily, the haemoglobin concentration will not rise as expected; this will also be the case in combined deficiency states.

The presence of underlying inflammation or malignancy may also lead to a poor response to therapy. Occasionally, malabsorption of iron, such as that seen in coeliac disease, may lead to a failure to respond. Finally, an incorrect diagnosis of iron deficiency anaemia should be considered in patients who fail to respond adequately to iron replacement therapy.

Intravenous and intramuscular iron preparations

Parenteral iron may be used when the patient cannot tolerate oral supplements, for example, when patients have severe gastrointestinal side effects or if the losses exceed the daily amount that can be absorbed orally (Box 1.4). The rise in haemoglobin concentration is no faster with parenteral iron preparations than with oral iron therapy.

Intramuscular iron sorbitol (a complex of iron, sorbitol and citric acid) injection was used as a parenteral iron replacement for many years, but was discontinued in the UK in 2003. Generally, around 10–20 deep intramuscular injections were given over 2–3 weeks. However, side effects were common and included pain, skin staining at the site of injection and arthralgia. Newer intravenous iron preparations include iron hydroxide sucrose (Venofer®) and iron dextran (Cosmofer®, may also be given IM) for use in selected cases and under strict medical supervision, for example, on a haematology day unit (risk of anaphylaxis or other reactions).

Alternative treatments

Blood transfusion is not indicated unless the patient has decompensated due to a drop in haemoglobin concentration and needs a more rapid rise in haemoglobin, for example, in cases of worsening angina or severe coexisting pulmonary disease. In cases of iron deficiency with serious ongoing acute bleeding, blood transfusion may be required.

Prevention

When absorption from the diet is likely to be matched or exceeded by losses, extra sources of iron should be considered, for example,

Box 1.4 Intravenous iron preparations

- Intramuscular iron sorbitol no longer available (severe reactions)
- Iron hydroxide sucrose and iron dextran are currently available in the UK
- Useful in selected cases
- Must be given under close medical supervision and where full resuscitation facilities are available
- A test dose is recommended before administration of the full dose

prophylactic iron supplements in pregnancy or after gastrectomy, or encouragement of breastfeeding or use of formula milk during the first year of life (rather than cows' milk, which is a poor source of iron).

Further reading

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