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PEER REVIEWED FEATURE
2 CPD POINTS

Iron deficiency anaemia

Causes, symptoms and treatment

LISA CLARKE MB BS, BMedSc; **ANTHONY J. DODDS** MB BS(Hons), FRACP, FRCPA

Iron deficiency anaemia remains a significant problem in Australia and has impacts on development, health and wellbeing. This review focuses on the causes, diagnosis and management of iron deficiency and provides some useful advice regarding iron replacement.

Key points

- **Iron deficiency is a significant problem in Australia.**
- **Iron deficiency can occur with or without anaemia.**
- **Measurement of serum iron in isolation is not a reliable screening test for iron deficiency. The diagnosis relies on the interpretation of iron studies.**
- **Iron deficiency results from a combination of an increased demand, decreased intake or absorption, and/or increased loss.**
- **Identifying and treating the underlying cause of iron deficiency are the most important aspects of management.**
- **Iron replacement with oral iron supplementation should be commenced in all patients with iron deficiency as first-line therapy.**

Iron deficiency is the most common nutritional deficiency worldwide, affecting more than two billion people, and it is the underlying cause of anaemia in 50% of cases.[1] Although the burden is greater in developing countries, iron deficiency with or without anaemia remains a significant problem in Australia. Iron deficiency results from a combination of increased demand, decreased intake or absorption, and/or increased loss. Chronic iron deficiency subsequently results in iron deficiency anaemia. Tissue effects of chronic iron deficiency such as glossitis and pharyngeal webs are now rarely seen in developed countries. The management of patients with iron deficiency involves identification and treatment of the underlying cause in addition to iron replacement.

BODY IRON STORES

At birth, a full-term baby is born with about 250 mg of stored iron. These stores are used during breastfeeding because breast milk only provides 0.15 mg of absorbed iron per day.[2] When oral intake of iron is adequate throughout childhood and adolescence, a net positive iron balance of about 0.5 mg per day results in the accumulation of 3 to 4 g of body iron by adulthood.[3] Two-thirds of these stores circulate as haemoglobin and a further quarter is stored as ferritin or haemosiderin. About 1 mg of iron is lost per day with up to an additional 1 mg lost per day in menstruating women.

IRON SOURCES

There are two types of dietary iron:

- haem iron – found in animal sources such

Dr Clarke is an Advanced Trainee in Haematology at St Vincent's Hospital, Sydney. Associate Professor Dodds is Senior Staff Specialist in Haematology and Bone Marrow Transplantation, Kinghorn Cancer Centre, St Vincent's Hospital, Sydney; and Associate Professor (Conjoint), School of Medicine, University of New South Wales, Sydney, NSW.

as red meat and, to a lesser extent, in poultry and fish
- nonhaem iron – found in eggs and plant-based sources such as nuts, cereals, bread, beans and vegetables.

About 50% of haem iron is absorbed into the body whereas only up to 10% of nonhaem iron is absorbed. Vitamin C enhances the absorption of nonhaem iron, whereas calcium inhibits the absorption of both haem and nonhaem iron. Gastric pH also influences iron absorption and is affected by the use of proton pump inhibitors, the presence of *Helicobacter pylori* and atrophic gastritis in the elderly. Table 1 highlights the recommended daily intake of iron in various age groups.[4] In practical terms, adults need to consume red meat two to three times per week to meet their weekly iron requirements.

TABLE 1. RECOMMENDED DAILY INTAKE (RDI) OF IRON ACCORDING TO AGE GROUP[4]

Age group	RDI (mg/day)
7 to 12 months	11
1 to 3 years	9
4 to 8 years	10
9 to 13 years	8
Boys 14 to 18 years	11
Girls 14 to 18 years	15
Men >18 years and women >51 years	8
Women 18 to 50 years	18
Pregnant women	27
Lactating women	9

IMPACT OF IRON DEFICIENCY

Iron deficiency has important consequences on development and a patient's general health and wellbeing. Iron deficiency in pregnancy is associated with an increased risk of low birth weight and maternal anaemia with its associated complications.[5] Children's mental and physical development can be delayed or impaired by iron deficiency and in adults it can result in fatigue with subsequent reduced productivity and behavioural issues.[2] Iron deficiency is also associated with impaired immune function at all ages, resulting in an increased risk of infection particularly upper respiratory tract infections. Iron deficiency anaemia results in the well-known symptoms of lethargy and dyspnoea on exertion.

DIAGNOSIS OF IRON DEFICIENCY ANAEMIA

The World Health Organization defines anaemia as a haemoglobin level of less than 130 g/L in men, less than 120 g/L in women and less than 110 g/L in pregnant women and children.[2]

In general, the diagnosis of iron deficiency can be made on serum iron studies, which are quick, easily accessible and inexpensive. The most reliable marker is serum ferritin. A low serum ferritin level of less than 15 µg/L is diagnostic of iron deficiency and levels between 15 and 30 µg/L are highly suggestive. However, ferritin is an acute-phase reactant so a normal level does not exclude iron deficiency. Therefore, the result should be interpreted in the context of additional inflammatory markers, primarily C-reactive protein (CRP) levels.

In the context of chronic inflammation, such as inflammatory bowel disease, iron deficiency is likely when serum ferritin levels are less than 50 µg/L. Care should be taken when interpreting serum iron levels because they exhibit significant diurnal variation, are altered by a fed or fasted state and are influenced by inflammation as the transferrin concentration, and therefore the serum iron level, falls in inflammatory states. Therefore, serum iron in isolation is not a reliable screening tool for iron deficiency.

Iron deficiency anaemia is the most likely cause of hypochromic microcytic anaemia (Table 2); however, iron deficiency can occur in the context of a normal full blood count. It is worth noting that iron studies should be performed when screening patients for a haemoglobinopathy because testing is best interpreted in the context of current iron studies. The Figure is an example of a blood smear from a patient with iron deficiency anaemia.

CAUSES OF IRON DEFICIENCY

The underlying causes of iron deficiency can be either physiological or pathological. Physiological iron deficiency occurs at times of increased iron requirements in response to periods of growth and development including infancy, adolescence and pregnancy. Pathological iron deficiency generally results from occult

TABLE 2. DIFFERENTIAL DIAGNOSIS OF HYPOCHROMIC MICROCYTIC ANAEMIA

	Iron deficiency	Anaemia of chronic disease	Haemoglobinopathy
Hb	N or ↓	↓	N or ↓
Serum iron	↓	↓	N
Ferritin	↓	N or ↑	N
MCV	N or ↓	N or ↓	↓
RCC	N or ↓	N or ↓	↑
Transferrin	↑	N or ↓	N

ABBREVIATIONS: Hb = haemoglobin; MCV = mean corpuscular volume; N = normal; RCC = red cell count.

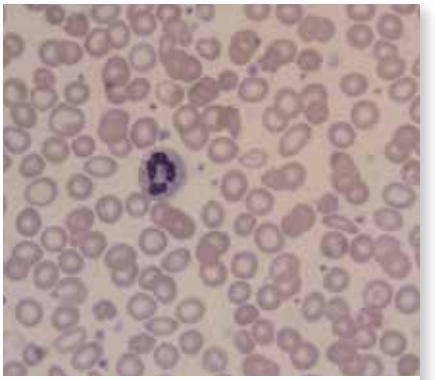


Figure. Light micrograph of a blood smear showing iron deficiency anaemia.

blood loss or malabsorption. The box discusses two cases of iron deficiency anaemia with different causes.

Physiological iron deficiency

In infants, low birth weight, exclusive breastfeeding and early consumption of cow's milk (before the age of 1 year) increase the risk of iron deficiency. Studies have found that about 15% of breastfed infants and 20% of infants with only cow's milk in their diet are iron deficient.[3] Adolescence marks the second period of rapid growth and development. This is exacerbated in women by the onset of menstruation and about 20% of young adolescent women are thought to be iron deficient.[6] Dietary changes often occur in this age group as adolescents search for autonomy and their choices are influenced by their peers.

A woman's total iron requirement increases by 1 g during pregnancy due to an increase in red cell mass and the development

EXAMPLES OF PATIENTS WITH IRON DEFICIENCY ANAEMIA

Case study 1

Ms TG was a 22-year-old university student who presented to the emergency department with a two-month history of progressive lethargy, light headedness and shortness of breath on exertion.

Ms TG denied any significant medical or family history, was a lifelong nonsmoker and did not consume any alcohol. She gave a history of menorrhagia with menstruation lasting seven days and being 'very heavy' for the first four days. She was not taking the oral contraceptive pill and had not sought any medical advice previously. She was also a vegetarian.

Ms TG was anaemic with a haemoglobin level of 64 g/L and hypochromic microcytosis (mean corpuscular haemoglobin [MCH] 14.4 pg, mean corpuscular volume [MCV] 56.2 fL). Her iron studies confirmed iron deficiency with the following results:

- iron level 2.2 mmol/L
- iron saturation 2%
- transferrin 4.5 g/L
- ferritin 3 µg/L.

She received one unit of packed red blood cells and an iron infusion without complications. She was discharged and advised to discuss optimisation with her GP including referral to a gynaecologist.

Case study 2

Mr AK was a 64-year-old retired plumber who presented to the emergency department with a two-week history of progressive shortness of breath on exertion and lethargy.

His medical history was significant for osteoarthritis, for which he took a sustained-release paracetamol tablet and ibuprofen as needed. He was an ex-smoker with a 15 pack-year history and he consumed about 10 standard drinks per week. On specific questioning, he said his osteoarthritis had been troubling him lately so he had been taking six to eight ibuprofen tablets per day.

Mr AK was anaemic with a haemoglobin level of 78 g/L and hypochromic microcytosis (MCH 18.2 pg, MCV 68.4 fL). His iron studies confirmed iron deficiency with the following results:

- iron level 2.8 mmol/L
- iron saturation 2.4%
- transferrin 4.1 g/L
- ferritin 12 µg/L.

Mr AK was commenced on a proton pump inhibitor, told to avoid NSAIDs and received an iron infusion. He also underwent an endoscopy. An ulcer on the lesser curve of the stomach was identified with evidence of active bleeding and treated accordingly.

of the fetal–placental circulation. Breastfeeding results in about 1 mg of iron loss per day; however, this is generally counterbalanced by lactation-induced amenorrhoea. Finally, the incidence of iron deficiency increases in the elderly due to impaired iron absorption secondary to the pro-inflammatory state associated with ageing.[7]

Pathological iron deficiency

Coeliac disease is the most common cause of malabsorption-associated iron deficiency. Although duodenal biopsy remains the gold standard for the diagnosis of coeliac disease, screening for anti-tissue transglutaminase (anti-tTG) IgA antibodies has an estimated specificity of 99% and sensitivity of 90%.[8] (These antibodies are directed towards the enzyme tissue transglutaminase, which is normally present in the gastrointestinal tract). As such, coeliac serology should be considered in the initial workup of iron deficiency in children and in adults with refractory iron deficiency. However, IgA levels should be measured to eliminate false negatives due to IgA deficiency.

The main cause of iron deficiency in premenopausal women is heavy menstrual blood loss defined as more than 80 mL of blood loss or menstruation lasting more than seven days. Coexisting malabsorption or gastrointestinal blood loss rarely occurs, but should be investigated in cases of persistent iron deficiency despite optimisation of iron replacement.

In men and postmenopausal women, gastrointestinal blood loss is the most common cause of iron deficiency and referral to a gastroenterologist for consideration of an endoscopy and/or colonoscopy is indicated in all patients. The cause of blood loss can range from gastric erosions secondary to NSAID use to colon cancer. One study has found that about 11% of all patients with iron deficiency anaemia detected in the primary care setting were subsequently found to have a malignancy of the gastrointestinal tract.[9] A capsule endoscopy may be considered in those with a normal endoscopy and colonoscopy. Faecal occult blood testing is not sufficient because it is unable to differentiate between the different causes of gastrointestinal blood loss.

In a small subset of patients, an underlying cause of iron deficiency cannot be found or patients are refractory to iron replacement defined by the failure of haemoglobin to rise by 10 g/L over four to six weeks of appropriate iron replacement. Referral to a haematologist should be considered for investigation of more obscure causes of iron deficiency such as disorders of iron regulation and functional iron deficiency. Functional iron deficiency can be seen in patients with end-stage renal failure and occurs when

adequate iron stores are available but are unable to be mobilised for red cell production.

TREATMENT

Treatment of patients with iron deficiency anaemia should be focused on addressing the underlying cause of the iron deficiency and replenishing iron stores. Increasing dietary iron intake alone is insufficient to treat cases of established iron deficiency. First-line therapy involves oral iron replacement in doses of 100 to 200 mg of elemental iron in two to three divided doses in adults and 3 to 6 mg/kg of elemental iron in children.[10] Reticulocytosis should occur within 72 hours of therapeutic iron replacement and haemoglobin levels should rise by about 20 g/L every three weeks.[10]

It is recommended that iron supplementation continue for three to six months once the haemoglobin level has normalised to improve iron stores. Gastrointestinal disturbances including nausea and constipation are responsible for the major side effects and in patients with mild iron deficiency the dosing interval can be increased to every second day to minimise these complications.

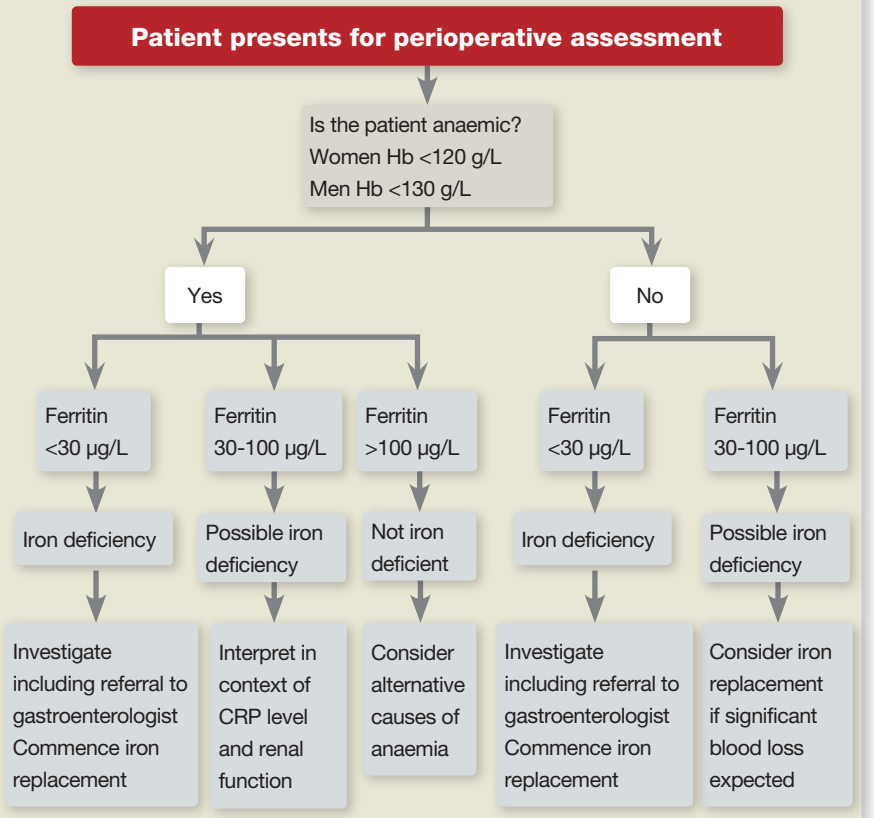
There are a number of different oral iron preparations available and all contain different amounts of elemental iron. It is important to ensure that patients are taking the appropriate preparation to achieve daily therapeutic doses of elemental iron.

Parenteral iron therapy should be reserved for patients:

- who are intolerant or noncompliant with oral preparations
- diagnosed with intestinal malabsorption
- who require rapid increases in haemoglobin
- with ongoing losses that exhaust the absorptive capacity.

In general, haemoglobin responds faster to intravenous iron therapy than to oral iron therapy. However, both methods achieve the same haemoglobin concentration in time.

PERIOPERATIVE ASSESSMENT OF IRON DEFICIENCY IN THE PRIMARY CARE SETTING[10]



ABBREVIATIONS: CRP = C-reactive protein; Hb = haemoglobin.

In Australia, three intravenous iron preparations are currently available – iron polymaltose, iron sucrose and ferric carboxymaltose. The major concern with intravenous iron replacement arose with the occurrence of anaphylactic reactions to iron dextran. This preparation is no longer available in Australia. To date, no cases of anaphylaxis have been reported in Australia to the currently available preparations; however, the data are limited.[11]

Iron polymaltose can be administered as a total dose infusion, but infusion times range from four to six hours. Iron sucrose use is limited to patients with chronic kidney disease, who are taking erythropoietin-stimulating agents and react to iron polymaltose. Ferric carboxymaltose given as an intravenous infusion has recently been listed on the PBS for patients with iron deficiency who cannot tolerate oral iron preparations. The major advantage of this preparation is that a single total dose can be administered within 30 minutes. Adverse reactions are rare and appear similar among the three preparations.

Adverse reactions include sensations of warmth or itching, rash, chest pain, dyspnoea, nausea or headache at the time of infusion. Occasionally minor self-limiting delayed arthralgias, headaches and fevers occur. It should be given in a hospital or clinic setting where access to resuscitation equipment is available.

Intramuscular iron replacement is best avoided because it is painful and associated with permanent skin scarring.[2]

Red cell transfusion

The transfusion of red cells should be reserved for patients with significant anaemia affecting end-organ function or when ongoing acute blood loss is expected.

SPECIAL CONSIDERATIONS

Pregnancy

Although pregnancy represents a time of increased iron demand, the National Blood Authority's obstetrics and maternity guidelines do not recommend the routine administration of iron supplementation to all pregnant women.[12] Instead they recommend the commencement of iron replacement once iron deficiency is diagnosed. To limit the development of gastrointestinal side effects, and therefore improve compliance, the guidelines recommend considering the use of lower iron doses (20 to 80 mg/day) if deficiency is diagnosed before the development of anaemia.

Intravenous iron replacement in pregnancy should be considered when haemoglobin and iron stores need to be restored rapidly or when oral iron supplementation is not tolerated. The risks of an iron infusion in pregnancy are the same as for the general population with the greatest concern being the rare but potentially dangerous anaphylactic reaction. As this potentially affects not only the mother but also the developing fetus, the benefits need to outweigh any potential risks. A recent European review has recommended the use of oral iron supplementation in the first trimester and then careful consideration of intravenous replacement in the second and third trimesters with the preference for intravenous replacement closer to delivery.[13]

Perioperative assessment

For every 100 mL of blood lost, the haemoglobin level drops by 2.5 g/L, 50 mg of iron is lost and 5 µg of ferritin is required to restore the loss. In elective surgeries where patients are at risk of significant blood loss the preoperative assessment of iron stores in the primary setting allows adequate time to optimise red cell mass and therefore prevent the complications of anaemia and avoid unnecessary red cell transfusion. This includes cardiothoracic, major orthopaedic, vascular and major general surgery. The flowchart is a useful guide for the perioperative assessment of iron deficiency in the primary care setting and has been adapted from the National Blood Authority's perioperative guidelines.[10]

CONCLUSION

In the appropriate clinical setting iron deficiency should be considered even in the absence of anaemia. The diagnosis relies on the correct interpretation of iron studies with ferritin as the most useful marker. In addition to iron replacement, identification and treatment of the underlying cause are essential for appropriate management. Oral and intravenous iron replacement achieve the same results; however, intravenous preparations more rapidly replenish haemoglobin and iron stores and therefore should be considered when timely replacement is required. Special considerations should be made in pregnancy and in the preoperative period to prevent the complications of anaemia and avoid unnecessary red cell transfusion. MT

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