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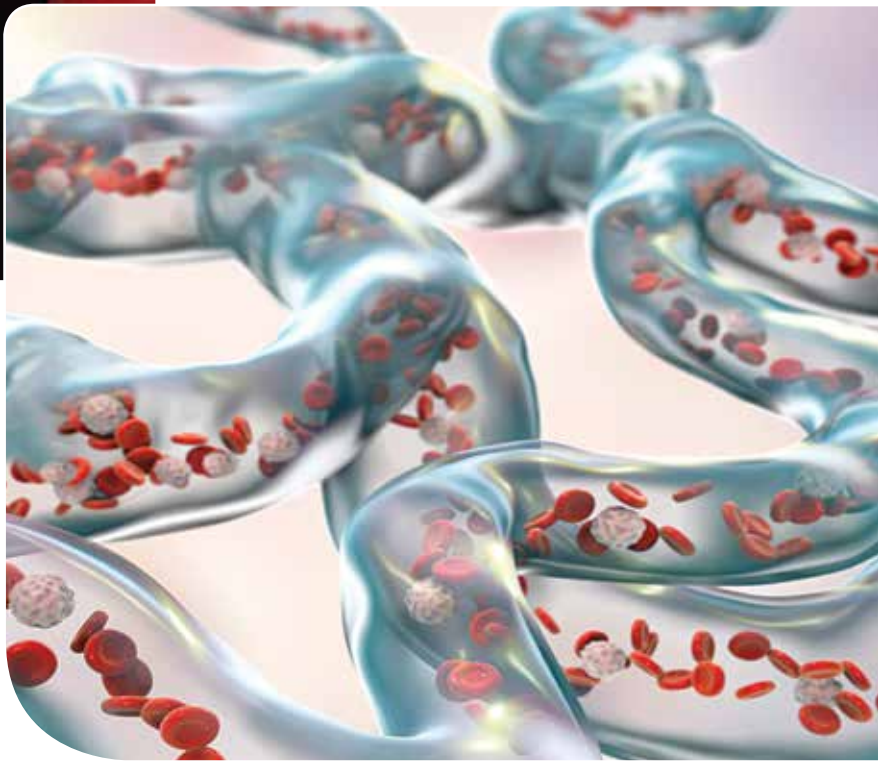

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PEER REVIEWED FEATURE

Iron deficiency anaemia in pregnancy

How best to treat, and why

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Pregnant women with iron deficiency anaemia (IDA) are at greater risk of blood transfusion, life-threatening bleeding, fetal growth restriction, preterm birth and perinatal death. Pregnancy-related IDA can usually be managed in a primary care setting with oral iron supplements, although sometimes intravenous iron is required. New maternity guidelines and clinical resources are available.

Anaemia in pregnancy is defined by the recently updated NHMRC maternity guideline as a haemoglobin (Hb) level of less than 110 g/L before 20 weeks' gestation or less than 105 g/L at or after 20 weeks' gestation.[1] Iron deficiency anaemia (IDA) is a condition characterised by both iron deficiency (diagnosed with a low serum ferritin) and anaemia. Varying thresholds for iron deficiency are used; however, a ferritin level of less than 30 mcg/L is widely accepted.[1] Iron deficiency (ID) alone is defined by a haemoglobin level that is within normal limits with a serum ferritin level below 30 mcg/L.[1] Iron deficiency is a precursor to IDA.

KEY POINTS

- Iron deficiency anaemia (IDA) is a common condition in pregnancy that can have significant adverse effects on the health of the mother and baby.
- Iron deficiency alone is defined by a haemoglobin level that is within normal limits with a serum ferritin level below 30 mcg/L and is a precursor to IDA.
- Routine screening for IDA by measuring haemoglobin level +/- ferritin level should occur at the first antenatal appointment and at 28 weeks' gestation.
- A haemoglobin level of less than 110 g/L before 20 weeks' gestation or less than 105 g/L at or after 20 weeks' gestation is considered abnormal.
- First-line treatment for IDA is oral iron supplementation. Intravenous iron supplementation should only be considered when oral iron therapy has failed, is not tolerated or rapid replacement is required to optimise iron stores and haemoglobin level.
- GPs are in a unique situation to identify, treat and monitor adherence to IDA treatment in pregnancy and postpartum to improve outcomes for the mother and baby.
- Excellent resources for clinicians and women are available from the Australian Red Cross Blood Service Toolkit for Maternity Blood Management (www.transfusion.com.au/maternity).

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The estimated prevalence of IDA among pregnant women in Australia is 11 to 18%, which equates to about 40,000 mothers affected each year.[2] Most IDA in pregnancy is related to the increased demands of pregnancy, although many women start pregnancy with iron deficiency with or without anaemia, mainly due to menstrual losses, previous pregnancies and/or dietary intake. Clinicians should always take a detailed patient history and consider other causes of inadequate iron absorption, inadequate oral intake or excessive iron loss.[3,4] If a pregnant woman has anaemia, appropriate further investigations include a full blood count, serum ferritin level and specific (fasting) tests for folate and vitamin B12 levels if the mean cell volume is high.[1] Thalassemia screening should also be considered, depending on the patient's ethnicity and mean cell volume.[5] Other causes of anaemia are beyond the scope of this article but should be considered when clinically appropriate.

Physiology and prevention of IDA

Iron demands increase in pregnancy due to maternal changes (with a 35% increase in red cell mass), the developing fetus (red cell mass and muscle) and the placenta.[6] This maternal iron deficit increases throughout advancing gestation, particularly in the third trimester.[6] The recommended daily dietary intake of iron in pregnancy is 30 mg/day.[7] Foods high in iron include lean red meat, fish and shellfish, poultry, iron-fortified breakfast cereals, eggs, cooked legumes such as chickpeas, lentils, kidney and lima beans and green vegetables such as broccoli, cabbage and spinach.[1]

Women who are particularly at risk of IDA and its consequences during pregnancy are those who have increased iron demands (e.g. multiple pregnancy), low dietary intake of iron (e.g. vegetarian, vegan and restricted eating patterns), an increased risk of blood loss (e.g. a history of postpartum haemorrhage or risk factors for it, blood transfusion, IDA or placenta praevia) or a short interpregnancy interval. Groups that are particularly at risk include teenagers, women of lower socioeconomic status, Indigenous Australian women, recent migrants and women for whom transfusion is not a medical option due to religious or ethical beliefs.[8,9]

Routine universal iron supplementation for pregnant women without ID or IDA is currently not recommended in Australia.[1] Pregnant women with risk factors for ID or IDA should be advised to follow a diet high in iron-containing foods and consider low-dose oral iron supplementation.[1] In pregnant women with iron deficiency alone, low-dose elemental iron (20 to 80 mg daily or alternate daily doses of 60 mg) should be considered.[9,10]

Maternal and fetal implications of iron deficiency anaemia

Women with IDA have increased levels of fatigue or malaise, lower performance at work and higher rates of depression, particularly postnatally.[4] Postpartum haemorrhage (≥500 mL of blood loss at birth) affects about 8% of all women giving birth.[11] Women with IDA have a higher risk of postpartum haemorrhage, increased severity of bleeding and needing a blood transfusion.[12] Although rare, women with IDA also have an increased risk of death from postpartum haemorrhage and women with severe anaemia have an increased risk of cardiac compromise.[13] Postnatal effects of IDA include reduced breastfeeding, higher rates of puerperal sepsis and poor wound healing.[12] Effects of IDA on the fetus and infant include low birthweight, preterm birth, being small for gestational age, childhood anaemia and perinatal death.[12,14,15] There is some evidence that iron deficiency in pregnancy may be associated with adverse neurodevelopment in offspring.[16]

Testing required for anaemia in pregnancy

Routine screening for anaemia is recommended at the first antenatal appointment, and at 28 weeks' gestation.[1] Repeat testing at 36 weeks may also be required for women who have symptoms or risk factors for IDA.[1] In addition, in areas where the prevalence of IDA is high, or in women who have risk factors for IDA, testing ferritin at the first antenatal appointment should be considered.[1,9]

Treatment of IDA in pregnancy

First-line therapy for IDA involves oral iron supplements.[1,10] Oral iron treatment options in Australia are outlined in Table 1. A holistic approach to therapy is recommended by the Australian Government pregnancy care guidelines.[1] Consideration of the availability of iron-rich foods appropriate to the woman's cultural practices and preferences should always be considered. A referral to a dietitian may be considered, but diet alone is insufficient to treat IDA, particularly in pregnancy.[8] In addition, discussing the benefits of treatment, possible side effects and ways to manage them and affordability of iron supplements may assist adherence.[1]

Oral treatment

Therapeutic oral iron supplementation, containing 100 to 200 mg of elemental iron daily, is considered first-line treatment for IDA in pregnant women.[9] The recently revised maternity guidelines, state that low-dose iron supplementation (60 to 100 mg) can be as effective as high dose, with fewer side effects.[1] If a rapid increase in haemoglobin is not required, alternate daily or intermittent (two to three times weekly) doses of 60 to 100 mg may lead to improved adherence and have a lower side-effect profile with similar results.[17] Women with iron deficiency alone may benefit from daily or alternate daily doses of 60 mg of elemental iron.[10] Most pregnancy multivitamins do not contain sufficient iron for treatment of IDA.[10] In addition, they may contain vitamins or minerals that impair absorption of oral iron.

As shown in Table 1, the elemental iron in supplements varies between brands,

TABLE 1. ORAL PREPARATIONS OF IRON AVAILABLE IN AUSTRALIA[10]

Brand name	Formulation/other active ingredients	Elemental iron content	Approximate cost*	Quantity (availability)†
Ferro-tab	Ferrous fumarate immediate release 200 mg	66 mg	$5 per 30 tablets	60 tablets (OTC or PBS restricted)
Ferro-f-tab	Ferrous fumarate immediate release 310 mg, folic acid 350 mcg	100 mg	$5 per 30 tablets	60 tablets (OTC or PBS restricted)
Ferro-grad†	Ferrous sulfate slow release 325 mg	105 mg	$18 per 30 tablets	30 tablets (OTC)
Ferro-grad C	Ferrous sulfate slow release 325 mg, vitamin C 500 mg	105 mg	$27 per 30 tablets	30 tablets (OTC)
Fefol	Ferrous sulfate, slow release 270 mg, folic acid 300 mcg	87 mg	$10 per 30 capsules	30 capsules (OTC)
Ferro-grad F§	Ferrous sulfate, slow release 250 mg, folic acid 300 mcg	80 mg	$16 per 30 tablets	30 tablets (OTC)
Maltofer tablets	Iron polymaltose 370 mg	100 mg	$30 per 30 tablets	30 tablets (OTC)
Ferro-liquid	Ferrous sulfate oral liquid 150 mg/5 mL	6 mg/mL	$1 per 100 mg (6 cents per mL)	250 mL bottle (OTC or PBS listed)
Maltofer syrup	Iron polymaltose oral liquid 185 mg/5 mL	10 mg/mL	$1.50 per 100 mg (15 cents per mL)	150 mL bottle (OTC)

Abbreviation: OTC = over the counter.
* Estimated costs from online and retail pharmacies in Australia, July 2019.
† Restricted benefit for treatment of a patient identifying as Aboriginal or Torres Strait Islander.
‡ This brand name was recently updated from 'Ferrogradumet'.
§ This brand name was recently updated from 'FGF'.

as does the cost. The aim is to use a supplement that is well balanced in terms of cost and tolerance. There is limited evidence comparing the tolerability and effectiveness of different types of oral iron supplements.[18]

Oral iron should ideally be given one hour before or two hours after food, to improve absorption. Medications that can interfere with absorption include calcium, antacids, thyroid medications and some antibiotics. Foods and drinks that may interfere with absorption include tea, coffee, milk chocolate and cola.[10] Common side effects of oral iron include constipation, diarrhoea, abdominal discomfort or pain, discolouration of stools and nausea.[19] Higher acidity in the stomach may improve iron absorption, hence vitamin C is included in some preparations, or orange juice could be used; however, the practical effect is marginal. Constipation may be treated or prevented with increased dietary fibre and/or fluids, plus a mild laxative. Abdominal discomfort and nausea may be reduced by taking iron at night or with food, and/or taking lower doses of iron less often.[10] Oral polymaltose comprises iron attached to a large carbohydrate moiety and is absorbed throughout the gastrointestinal tract. It is said to be better tolerated than iron salts, and in contrast to other iron supplements, is best taken with food.

Oral iron should be continued until the haemoglobin is in the normal range, and for six to eight weeks after this time, to correct iron stores. Haemoglobin levels are expected to improve by about 20 g/L every three weeks.[3]

A survey of women in Australia who were pregnant or had recently given birth found that 80% initially took the iron preparations prescribed for them, but 42% did not inform their clinician when they ceased supplementation. Reasons for stopping included forgetfulness and side effects, with a few women stating cost was a factor.[20] Discussion with care providers improved adherence.[20] Patient information leaflets can be used if language is a barrier. Leaflets in a variety of languages are available from the Australian Red Cross Blood Service.[10]

Reviewing treatment efficacy with repeat haemoglobin measurement is recommended three to four weeks after starting treatment. Women with IDA who do not respond adequately to oral therapy or who are unable to tolerate oral therapy, those with severe anaemia or those presenting late in the pregnancy should be given intravenous (IV) treatment.[9] Women who do not respond adequately to oral or IV therapy should be reviewed by an obstetrician, an obstetric medicine physician or a haematologist.

Intravenous iron treatment

Use of IV iron in Australia has increased rapidly in women of reproductive age with recent reports suggesting it is effective

TABLE 2. COMPARISON OF INTRAVENOUS IRON PREPARATIONS AVAILABLE IN AUSTRALIA[23]

	Iron sucrose	Iron polymaltose	Ferric carboxymaltose	Ferric derisomaltose
Brand name	Venofer	Ferrosig	Ferinject	Monofer
Elemental iron concentration	20 mg/mL	50 mg/mL	50 mg/mL	100 mg/ml
Infusion time for maximum dose	15 minutes	4 to 5 hours	15 minutes for dose of 500 to 1000 mg Do not exceed single doses of 1000 mg, or more than 1000 mg a week	20 minutes for doses up to 1000 mg 30 minutes for doses exceeding 1000 mg Do not exceed single doses of 1500 mg
Approximate cost	$40 per 500 mg	$20 per 500 mg	$150 per 500 mg	$150 per 500 mg
PBS subsidised	Yes	Yes	Yes	Yes

therapy for both IDA and iron deficiency without anaemia.[21,22] The IV iron formulations available in Australia are shown in Table 2.[23] Newer preparations such as ferric carboxymaltose and ferric derisomaltose have shorter infusion times, compared with the older preparations such as iron polymaltose. However, the newer preparations are more expensive in terms of direct medication costs (Table 2), although this cost may be offset by reduced time and costs for administration. This rapid uptake in IV iron use has occurred with limited clinical trial evidence of better maternal and clinical outcomes (as distinct from haematological parameters) or cost-effectiveness.[23]

A recent meta-analysis found that intravenous iron compared with oral iron in pregnancy was associated with a higher maternal haemoglobin level at birth, a nonclinically significant higher birthweight, and a lower rate of gastrointestinal side effects.[24] A further meta-analysis comparing the effects of IV iron and oral iron on blood transfusion rates is due to be published shortly.[25] There is insufficient knowledge of the effect of IV iron on important outcomes such as health-related quality of life or maternal, fetal and neonatal outcomes including breastfeeding rates.

It is important to note that IV iron may have side effects including allergic reactions and, rarely, anaphylaxis.[23] The rate of moderate or severe adverse reactions requiring treatment or discontinuation of IV iron has been reported as 1.4% for iron polymaltose, 0.8% in iron sucrose and 0.36% for ferric carboxymaltose.[23] Skin staining, due to extravasation, has led to a number of notifications to medical indemnity organisations; it may be permanent, although some cases have been treated with laser. IV iron is contraindicated in the first trimester. Parenterally administered iron preparations can cause hypophosphataemia, which in most cases is transient and without clinical symptoms. Patients should be given written information about potentially serious side effects before the administration, and clinicians should take steps to reduce these complications.[10]

Postpartum

The role of iron supplementation and need for follow up should be considered for all women after birth, especially when there has been postpartum haemorrhage or IDA in pregnancy.[10] A full blood count and iron studies, when required, should ideally be performed before a woman's six-week postpartum check, so that a timely action plan may be made. A recent systematic review of randomised trials found that haemoglobin concentrations at six weeks postpartum were almost 10 g/L higher in women who received IV iron compared with those taking oral iron.[26] As such, IV iron may be considered a suitable treatment for significant postpartum IDA; however, the clinical importance of this increase in haemoglobin level is not known.

Where can I obtain more information?

Further information for clinicians and patients can be obtained from the Australian Red Cross Blood Service Toolkit for Maternity Blood Management website.[10] This includes patient information leaflets about how to take oral iron tablets, health professional and patient information on intravenous iron, and a haemoglobin assessment and optimisation action plan. The site links to the recently released iTransfuse app and a BloodSafe e-learning course, both of which are excellent resources for clinicians.[10] The UK guidelines on the management of iron deficiency in pregnancy have been released recently and also provide useful information.[27]

Conclusion

IDA is a common pregnancy-related problem encountered by GPs, and all pregnant women should be screened and treated for IDA during pregnancy. Routine oral iron supplementation is not recommended. However, women at high risk for IDA should be tested for iron deficiency with serum ferritin. Processes should be in place to follow up results and to review adherence and response to therapy. IV iron therapy may be considered if there is insufficient response to oral iron therapy in patients with IDA after adherence is ensured. Recognition and treatment of IDA in pregnancy (or preferably before pregnancy) may improve health outcomes for mothers and their babies in the short and long term. MT

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Iron deficiency anaemia in children

A practical guide for management

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This practical guide outlines an approach for the diagnosis, treatment and follow-up of children with iron deficiency anaemia, a common clinical problem seen by GPs and paediatricians.

The bulk of the body's iron – 70 to 80% – is bound to the haem protein, haemoglobin, in red blood cells, and myoglobin, in muscle cells. Of the remainder, most is bound to the iron-storage protein ferritin and the iron-storage complex haemosiderin, and a tiny proportion (2 to 3%) is bound to enzymes such as the cytochromes. Consequently, changes to red blood cells are typically the first sign of iron deficiency.

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Iron absorption in the digestive tract is upregulated by iron deficiency, hypoxia and increased erythropoiesis, and decreased in inflammation, infection and iron repletion. The daily iron requirement changes with age. In healthy adults and older teenagers who have stopped growing, about 5% of daily requirements are derived from dietary sources (1 to 1.5 mg) to compensate for daily iron lost through the gastrointestinal tract, the skin and menstruation in females; iron recycled from the breakdown of old red blood cells provides the remaining 95%. However, the diet needs to provide 30% of the daily iron requirement in growing children (Table 1), particularly in the first few years of life and in adolescence, because of the increase in body mass that includes muscle and haemoglobin.[1]

Iron deficiency (ID) is the most common nutritional deficiency in children and iron deficiency anaemia (IDA) is the most common cause of anaemia in children in both developed and developing countries, with significant adverse health consequences.[2] It is most prevalent among toddlers and preschoolers, with a much higher prevalence among Indigenous children.[3] The prevalence of IDA among children one to five years of age in the US

KEY POINTS

- Iron deficiency anaemia in children is common and is most prevalent among toddlers and preschoolers.
- Dietary deficiency is the most common cause; a small number of patients will need investigations for other causes.
- Serum iron must not be used to assess iron stores; ferritin provides the most useful information about iron stores.
- Oral iron therapy is the most appropriate treatment for most patients; intravenous iron is indicated for a select few.
- The rate of haematological response is similar for oral and intravenous iron.
- Intravenous iron is not appropriate for iron deficiency without anaemia.
- Most children with iron deficiency anaemia do not need tertiary haematology care, and can be managed confidently by their GP or paediatrician.

is estimated to be 1 to 2%.[4] A study of 678 preschoolers (9 to 62 months of age) in Sydney in the 1990s showed the prevalence of ID was 2.8% and IDA 1.1%; children between two and three years of age had the highest prevalence of IDA.[5]

Causes of iron deficiency anaemia in children

Inadequate dietary intake

Inadequate dietary intake is by far the most common cause of IDA. The inadequate intake of iron-rich foods that accompanies excessive cow's milk intake in 'milkoholic' toddlers and preschoolers is the most common cause of IDA in children. Although it is rich in calories and other nutrients, cow's milk contains no iron; however, children drinking iron-fortified milk-based formula are usually iron replete. Early introduction of cow's milk before 12 months of age is also a risk factor for IDA.

Premature infants or infants born to mothers with severe iron deficiency may be born with lower iron stores than those born at full-term and are at risk of early-onset IDA if they are not given supplemental iron in the first few months of life. Children who are fussy eaters or on restricted or exclusion diets are also at risk, including those with developmental delay, autism and vegetarian or vegan diets. They may also be deficient in other micronutrients, such as vitamin B12.

Blood loss

In contrast to adults, blood loss is an uncommon cause of IDA in children. Sick and premature infants are at risk of depleted iron stores early in life owing to multiple blood tests and other haemorrhagic events such as surgery. Young children with cow's milk protein intolerance present with IDA and a low plasma albumin level (with clinical oedema in some) because cow's milk protein-induced enteropathy results in gastrointestinal blood and protein loss.

Other causes of gastrointestinal blood loss include inflammatory bowel disease, *Helicobacter pylori* gastritis and anatomical or vascular abnormalities that may bleed slowly. Excessive menstrual blood loss is a common risk factor for IDA in adolescent females.

Iron malabsorption

Iron is absorbed through the duodenum, and iron malabsorption is uncommon. Malabsorption may occur in disorders of the upper gastrointestinal tract such as coeliac disease, Crohn's disease and surgical resection of the proximal small bowel.

Clinical features of iron deficiency anaemia

The presenting clinical features of iron deficiency anaemia in children may include the following:

- The child appears pale but is usually otherwise asymptomatic if the anaemia is not severe. Even when IDA is severe (haemoglobin < 50 g/L), many young children remain seemingly asymptomatic due to their compensatory ability.
- Some children may present with lethargy, irritability and anorexia, and a small number may appear very unwell, particularly if there is co-existing infection.
- Adolescents do not compensate as well and generally present earlier with lethargy, shortness of breath or syncope.
- Pica, most common in younger children with IDA, is the craving for eating nonfood items such as dirt, rocks, soap, paper or chalk. The underlying mechanism is unknown.
- Short-term neurocognitive changes may occur in young children with severe IDA, most commonly presenting with irritability in some young children;[6] however, evidence showing long-term negative outcomes is lacking.[4]
- Cerebral vein thrombosis is rarely associated with IDA due to an unclear mechanism.[7,8]

Diagnosis

History and examination

Children in whom IDA is suspected should be assessed for a potential cause. A detailed history forms part of the diagnostic work-up and helps direct further investigations if indicated.

A history guided by the patient's age is essential to assessing causes and risk factors for IDA. It should include the perinatal

TABLE 1. RECOMMENDED DAILY DIETARY INTAKE OF IRON FOR CHILDREN IN AUSTRALIA*

Life stage or sex	Age group	Estimated average daily requirement†	Recommended iron intake
Infants	7 to 12 months	7 mg daily	11 mg daily
Children	1 to 3 years	4 mg daily	9 mg daily
	4 to 8 years	4 mg daily	10 mg daily
Boys	9 to 13 years	6 mg daily	8 mg daily
	14 to 18 years	8 mg daily	11 mg daily
Girls†	9 to 13 years	6 mg daily	8 mg daily
	14 to 18 years	8 mg daily	15 mg daily

* Adapted from nutrient reference values for Australia and New Zealand (www.nrv.gov.au/nutrients/iron).
† Estimated average requirements are based on the need to maintain a normal, functional iron concentration, but only a small store (serum ferritin concentration of 15 mcg/L).
† Assumption that all girls >14 years of age menstruate and girls <14 years of age do not.

history in young children, a detailed dietary history, any history of gastrointestinal symptoms and menstrual history in adolescent females. A family history of coeliac disease or thalassaemia, for example, should also be explored.

The physical examination may yield features of anaemia and its complications, if present. There may be signs to suggest the underlying cause, such as peripheral oedema in a toddler with cow's milk protein intolerance. Invasive rectal and vaginal examinations are not appropriate in children and adolescents. Most often, the cause of IDA is not apparent on examination.

IRON STATUS: DEFINITIONS

Iron deficiency anaemia (IDA)
Inadequate iron for physiological functions resulting in reduced production of haemoglobin; i.e. a reduced ferritin level with microcytic hypochromic anaemia (low mean corpuscular volume with a low mean corpuscular haemoglobin level).

Iron deficiency
Inadequate iron for physiological functions with mild impact on red blood cells before anaemia develops; i.e. a reduced ferritin level with microcytic hypochromic red cell indices but a normal haemoglobin level – a precursor to IDA.

Iron depletion
Reduced or depleted iron stores but adequate iron for physiological functions; i.e. an isolated reduced ferritin level without other changes.

PARAMETERS DEFINING IRON STATUS

	Haemoglobin level	Mean corpuscular volume	Mean corpuscular haemoglobin level	Ferritin level
IDA	Low	Low	Low	Low
Iron deficiency	Normal	Low	Low	Low
Iron depletion	Normal	Normal	Normal	Low

Investigations

Basic screening investigations for every child with suspected iron deficiency comprise a full blood count and blood film, reticulocyte count, serum ferritin level and biochemical tests including plasma albumin level. IDA is defined by microcytic hypochromic anaemia and a low ferritin level (Box). The extent of the workup is dependent on the patient's history and characteristics.

Lead level should be considered in children displaying pica, and levels of other micronutrients such as vitamin B12 should be checked in patients with very restricted diets.

It would be appropriate to initiate screening tests such as a coagulation screen and von Willebrand studies to test for an underlying bleeding disorder in adolescent females with menorrhagia and IDA. Most children with IDA do not initially require endoscopy, unless the history suggests gastrointestinal disease.

Interpretation

Full blood count, blood film and reticulocyte count

In IDA, the full blood count shows microcytic hypochromic anaemia with the characteristic blood film features of anisocytosis (red blood cells of different sizes), ovalocytes, elliptocytes and pencil cells (Figure). Reticulocytes (polychromasia on the blood film) are typically reduced.

The main differential diagnoses for microcytic hypochromic anaemia are thalassaemia and anaemia of chronic disease but the red cell distribution width is usually not increased in these, and blood film features could help differentiate them from IDA.

Serum ferritin

Serum ferritin is the most useful test in assessing iron stores or iron status. A reduced ferritin level always indicates reduced iron stores. As it is an acute-phase reactant, a normal ferritin level does not exclude iron deficiency; in this case, the patient's clinical characteristics,

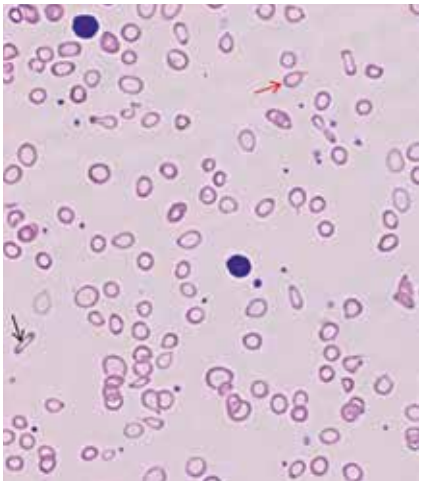

Figure. Blood film of a two-year-old child with severe iron deficiency anaemia (haemoglobin, 21g/L; mean corpuscular volume, 46fL) showing microcytic, hypochromic red cells, pencil cells (black arrow) and ovalocytes (red arrow).

history and haematological features (and blood film) would usually provide enough information for the diagnosis of IDA to be made.

The rest of the iron studies panel (i.e. serum iron, transferrin and transferrin saturation) provides little, if any, useful information in assessing iron stores and is frequently misinterpreted, leading to unnecessary iron treatments, further tests and parental anxiety. Many young children who have never been iron deficient have been unnecessarily treated because of a low serum iron level. The serum iron level varies over the course of the day and is lowered in response to inflammation and infection. It must not be used to diagnose iron deficiency; its main use is in assessing iron poisoning or overdose.

The level of serum ferritin that is adequate or normal in healthy children is dependent on the patient's age and dietary intake. Many pathology laboratories set their reference range limits for serum ferritin between 20 to 30mcg/L and 300 to 350mcg/L, which are inappropriately high cut-offs for children. In children without haematological features of iron deficiency, a serum ferritin level of greater than 10mcg/L is adequate (based on the authors' experience).

Results within the normal ranges for haemoglobin level, mean corpuscular volume, mean corpuscular hemoglobin level and red cell morphology indicate that there is enough iron for physiological needs even when the level of stored iron (ferritin) is low. This scenario is neither uncommon nor abnormal and is most commonly seen during periods of rapid growth in children who have enough dietary iron to meet their physiological needs but not enough to put significant amounts into stores (i.e. they have depleted iron stores).

Treatment

Blood transfusion

Blood transfusion is rarely required to treat IDA, as development of the condition is nonacute. The indication for transfusion is dependent on symptoms rather than the level of haemoglobin.

Most young children with severe IDA handle the anaemia well even when their haemoglobin level is less than 50g/L. Those who are not coping with the anaemia should be referred to hospital for assessment and possible blood transfusion. Older adolescents are more likely to be symptomatic with severe anaemia, particularly if bleeding is ongoing (e.g. females with IDA and menorrhagia), and may benefit from blood transfusion.

Iron therapy: oral *vs* intravenous *vs* intramuscular

Oral iron is the most appropriate treatment for most children with IDA or ID. The recommended dosage of 3 to 6mg/kg daily is based on the amount of elemental iron, and is given in divided doses or once daily with food or drink (liquid iron may cause a brown stain on teeth). Crushed iron tablets or granules from opened capsules may be sprinkled on food for young children (off-label use). Single element preparations (e.g. ferrous sulfate, ferrous fumarate and iron polymaltose) are recommended. The amount of iron in iron-containing multivitamins is generally inadequate for the treatment of IDA. Table 2 shows some of the commonly available preparations that are available over the counter.

It is advisable to continue treatment for a further three to four months after correction of anaemia (based on a normal haemoglobin level) in order to replenish iron stores; patients taking the lower dosage of 3mg/kg/day should have treatment extended to six months. Iron deficiency anaemia is likely to recur if iron stores are not adequately restored. Patients who have undergone a blood transfusion should also receive iron treatment at this dosage and for this duration.

Intravenous (IV) iron is indicated in selected patients, including those in whom oral iron has been ineffective or for whom oral administration is too difficult (e.g. children with autism). The dosage of IV iron should include an amount to replenish iron stores. The required dosage is determined from the following formula (Ganzoni method).[9] Local paediatric services should be consulted if guidance is needed.

Cumulative iron dose (mg) = body weight (kg) x (target haemoglobin – actual haemoglobin [g/L]) x 0.24 + iron stores (mg)

Where:

- *target haemoglobin = 130g/L for body weight < 35kg, and 150g/L for body weight ≥ 35kg*
- *iron stores = 15mg/kg body weight for body weight < 35kg, and 500mg for body weight ≥ 35kg.*

There is a small risk of anaphylaxis and of skin staining (from extravasation) with IV iron.

Intramuscular iron injections are infrequently used as they are painful, usually more than one injection is needed and brown staining of the skin around the injection sites may last for months to years. IV iron is not appropriate for children without anaemia. Children with iron depletion should be treated by increasing dietary iron or supplementation with oral iron.

Address the cause

To avoid recurrence of IDA, the cause of iron deficiency should be addressed in addition to the patient receiving iron therapy. Dietary advice to ensure infants and toddlers have an adequate iron-rich food intake and avoid an excessive intake of cow's milk is particularly pertinent for families. Adolescent females with menorrhagia may require hormonal therapy or treatment with antifibrinolytics to control menstrual bleeding.

Follow up

A full blood count and reticulocyte count seven to 10 days after initiating treatment is recommended to check the patient's adherence to oral iron therapy. An early reticulocyte response is expected before the haemoglobin level improves.

Haemoglobin increments of 30 to 50 g/L can be expected in children with severe IDA after two to four weeks of treatment if they are adherent with oral therapy. Once the haemoglobin level has normalised, iron treatment is continued for a further three to six months. The full blood count and serum ferritin level are rechecked at the end of the treatment period. Further testing beyond that is not necessary for those with dietary-related IDA if an adequate diet is maintained.

The rate of correction of anaemia after IV iron therapy is similar to that seen with oral iron. IV iron may be more convenient in some circumstances but the rate of response is not different to that with oral iron.

Further investigations

Further investigations are indicated if iron malabsorption or blood loss are suspected at presentation or during the course of treatment. Patients who are slow to respond to treatment despite compliance with the correct dosage of oral iron may have coeliac disease (malabsorption) or gastrointestinal bleeding. Further tests may include coeliac serology, a urea breath test or a stool antigen test for *H. pylori*, or a faecal occult blood test.

Patients with recurrent IDA within a few months of completing treatment may be bleeding from the gastrointestinal tract, or may not have received enough iron to replenish iron stores or may not have had the underlying cause addressed. Thalassaemia and haemoglobin variants such as haemoglobin E should be considered if microcytic hypochromic features persist despite iron treatment, particularly if the patient's ferritin level has normalised.

Referral

Patients with severe anaemia should be referred to a hospital for assessment, particularly if they have symptoms such as dizziness or shortness of breath. Severe anaemia is usually defined as:

- a haemoglobin level of less than 50 g/L in prepubertal children
- a haemoglobin level of less than 70 g/L in adolescents.

Patients with suspected gastrointestinal disease such as coeliac disease, inflammatory bowel disease or gut bleeding should be referred to a gastroenterologist for further evaluation. Adolescent girls with menorrhagia should be referred to a gynaecologist if their periods are difficult to manage. A referral to a dietitian may be helpful for some families.

TABLE 2. IRON FORMULATIONS AVAILABLE IN AUSTRALIA AND COMMONLY USED IN CHILDREN AND ADOLESCENTS FOR THE TREATMENT OF IRON DEFICIENCY ANAEMIA

Formulation	Brand name	Elemental iron content	Comment
Oral*			
Ferrous sulfate	Ferro-grad†	105 mg	
	Ferro-grad C (ascorbic acid 500 mg)	105 mg	
	Fefol (folic acid 300 mcg)	87 mg	
	Ferro-liquid	6 mg/mL	
Ferrous fumarate	Ferro-tab	66 mg	
Iron polymaltose	Maltofer tablets	100 mg	Off-label use if in children under 12 years of age
	Maltofer syrup	10 mg/mL	Off-label use if in children under 12 years of age. Contains 3.25 mg/mL ethanol
Intravenous‡			
Ferric carboxymaltose	Ferinject	50 mg/mL	Off-label use if in children under 14 years of age
Iron polymaltose	Ferrosig	50 mg/mL	
Iron sucrose	Venofer	20 mg/mL	Off label. Safety in children has not been established.

* Dosing based on elemental iron (3 to 6 mg/kg daily).
† This brand nae was recently updated from 'Ferro-gradumet'.
‡ See individual formulations for maximum dosage and infusion rates.

Prevention

Dietary iron deficiency is avoidable with healthy eating, and education of parents on appropriate feeding would likely reduce the prevalence of iron deficiency in young children. As mentioned above, preterm infants should receive iron supplementation for the first few months of life. Also consider iron supplementation for children with restricted diets (e.g. those with autism or on vegetarian or vegan diets) and early intervention in girls with heavy menstrual periods.

Conclusion

Iron deficiency anaemia in children is common and most children can be confidently managed by the family GP or general paediatrician; only a small number with severe anaemia require tertiary care. Unlike adults, inadequate dietary iron is the most common cause of IDA in children. The full blood count and serum ferritin are the most useful tests; serum iron must not be used to assess iron stores or status. Oral iron is the most appropriate therapy and the underlying cause of IDA should be addressed to avoid recurrence. MT

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COMPETING INTERESTS: None.

Iron deficiency anaemia in adults

An update

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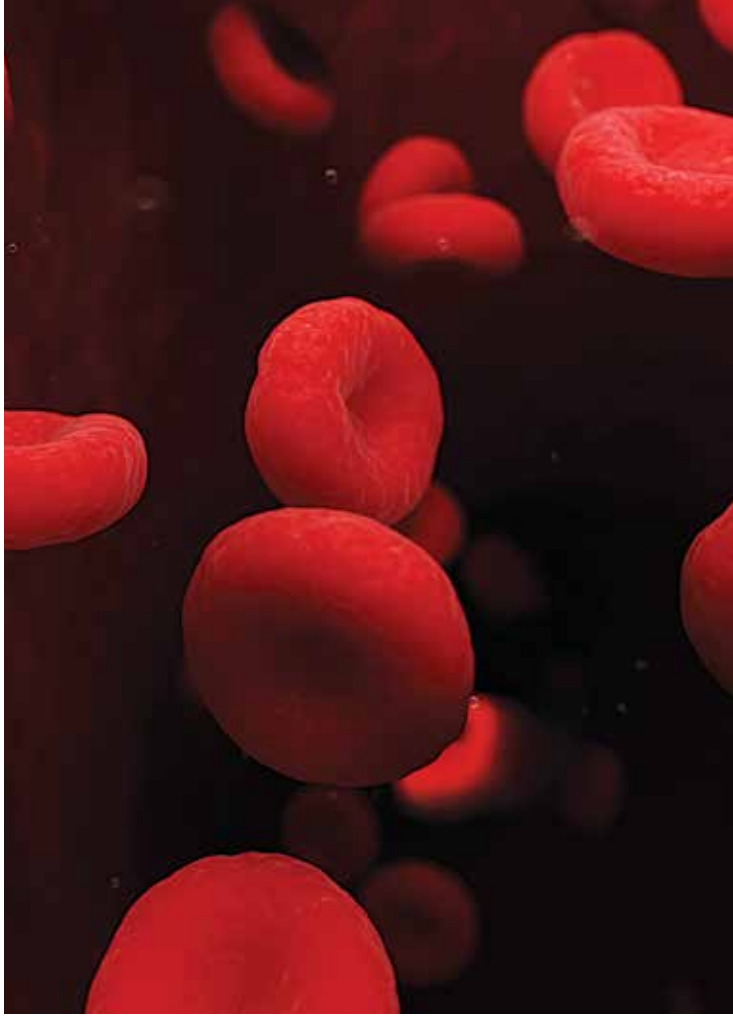
Iron deficiency, and therefore iron deficiency anaemia, may result from an increased physiological requirement for iron, insufficient dietary intake, reduced absorption or excessive loss. The gastrointestinal tract is the most important source of excessive iron losses in men and postmenopausal women.

KEY POINTS

- Iron deficiency anaemia (IDA) is commonly seen in primary care and management principles include: making a confirmed diagnosis of IDA; identifying the cause of iron deficiency; correcting the deficiency.
- Serum iron level is not a useful marker for iron deficiency; the most specific serological marker for iron status is serum ferritin.
- Iron deficiency may result from increased physiological requirements, insufficient dietary intake, reduced iron absorption or excessive iron losses.
- The gastrointestinal tract is the most important source of pathological iron losses in men and postmenopausal women.
- In menstruating women the most common cause of IDA is menstrual loss; however, clinicians should be vigilant for coexisting gastrointestinal causes.
- Endoscopic investigation with gastroscopy and colonoscopy is indicated in medically fit men and postmenopausal women to exclude a gastrointestinal cause.
- Wireless capsule endoscopy may be considered if the cause of IDA remains obscure after gastroscopy and colonoscopy.
- Oral iron supplementation is practical, safe and well-tolerated. Alternate-day dosing can improve tolerability and iron absorption.
- Intravenous (IV) iron infusion is indicated in select patients, including those who are intolerant of or refractory to oral supplementation. Newer IV formulations can provide adequate iron replenishment in one dose with short infusion times and excellent safety profiles.



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Iron deficiency anaemia (IDA) is frequently encountered in clinical practice and may be a difficult problem to navigate. It can have a significant impact on cognition, academic achievement, work productivity, exercise tolerance and quality of life. Iron deficiency, even without anaemia, can cause fatigue, cognitive impairment and mood changes, and in patients with heart failure can worsen the degree of heart failure. When a diagnosis of iron deficiency is made a cause must be sought and, where possible, addressed. Replenishment of iron stores with oral iron supplements is appropriate for most patients, but in those who are intolerant of iron or in whom rapid correction of iron deficiency is required intravenous formulations may be indicated.

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Iron metabolism

Iron plays a central role in oxygen transport, intracellular oxygen delivery for aerobic glycolysis, DNA synthesis, and immune function. The human body contains 3 to 4 g of iron, with about two-thirds found in the red blood cells. Iron status is closely regulated through hormonal regulation. Central to this is hepcidin, a master regulator hormone secreted by the liver.

After ingestion, dietary iron is absorbed into the enterocytes of the duodenum and proximal jejunum, and exported from enterocytes into the bloodstream via ferroportin, a transporter protein. When iron stores are replete, hepcidin is released and binds to and degrades ferroportin. This prevents the entry of iron into the bloodstream. If this feedback system fails, for example through impaired hepcidin production in hereditary haemochromatosis, iron overload occurs and leads to end-organ damage. Dysregulation of hepcidin can also occur in inflammatory states. The induction of hepcidin can be attributed to the upregulation of interleukin-6 (IL-6) in acute inflammation through the JAK/STAT (Janus kinase/signal transducers and activators of transcription) 3 signalling pathway. This is the mechanism implicated in anaemia of chronic disease, which is commonly observed in patients with chronic infections, malignancies, trauma and chronic inflammatory disorders.

In healthy men and postmenopausal women only 1 to 2 mg of iron is required each day to replenish physiological losses through the shedding of enterocytes, sweat and blood loss. The daily dietary requirement of iron, however, may be much higher due to low fractional absorption of iron in the small intestine. Once absorbed, up to 70% of iron goes towards haemoglobin synthesis, 10% enters the reticuloendothelial system and the remainder is bound to transferrin proteins. Iron is stored primarily as the protein-iron complex ferritin. Ferritin is found in the liver, spleen, bone marrow and skeletal muscles.

Dietary factors in iron absorption

Dietary sources of iron can usefully be classified as haem and non-haem types. Animal products provide haem iron, which is absorbed five times more easily than non-haem iron, found in vegetables, legumes and grains. As a result, much higher quantities of non-haem iron are required to meet physiological needs. Vegetarians and vegans are therefore more likely to have iron deficiency and should be encouraged to consume items including eggs, mushrooms and nuts, which have higher concentrations of non-haem iron.

Iron absorption can also be influenced by other dietary factors. Citrate and ascorbate form complexes with iron that increase absorption, and tannates in black tea decrease absorption. Proton pump inhibitors may reduce the absorption of iron, as a low gastric pH is important to facilitate iron transport.

Definitions of anaemia and iron deficiency

Anaemia is defined by a haemoglobin concentration below the age and sex-defined normal range. Iron deficiency is an important cause of anaemia, but other causes should also be considered. IDA is typically characterised by a microcytic and hypochromic blood film, although this blood film picture may also be seen in other clinical scenarios, such as in people with thalassaemia.

The gold standard for diagnosis of iron deficiency is a bone marrow biopsy with Prussian blue staining. Fortunately, this is rarely required in clinical practice and iron status can usually be determined with noninvasive tests.

Iron deficiency is typically characterised by a low serum ferritin level (<30 mcg/L) and transferrin saturations of less than 15%. (Some laboratories use community-derived reference levels of ferritin, resulting in lower normal ranges; however, these reference populations include some patients who are iron deficient and use of the lower reference range may result in undertreatment of patients who could benefit from iron supplementation and/or investigation for a cause of iron deficiency.) Unfortunately, the diagnosis of iron deficiency is sometimes less clear. Iron deficiency may be present without anaemia. During progressive iron depletion, anaemia may be a delayed finding.

Diagnosis of iron deficiency anaemia

Serum iron concentration is not a useful marker for iron deficiency. The most specific serological marker for iron deficiency is a low serum ferritin concentration. A summary of how to interpret iron studies is provided in Table 1. The finding of a low serum ferritin level always indicates iron deficiency. However, a normal (or even elevated) ferritin level does not exclude iron deficiency. Ferritin is an acute-phase reactant, and acute or chronic inflammation and malignancy may result in an elevated serum ferritin level that potentially masks underlying iron deficiency. Hence, it is important to consider the clinical context at the time of interpretation. In these situations, a low transferrin saturation supports a diagnosis of iron deficiency.

The finding of a low serum ferritin level always indicates iron deficiency. However, a normal (or even elevated) ferritin level does not exclude iron deficiency

The soluble transferrin receptor (sTfR) has been proposed as a specific marker for iron deficiency; however, this test is not widely available. sTfR level increases with erythropoiesis in the setting of iron deficiency, and, unlike ferritin, remains normal in chronic disease and inflammation. sTfR level is not superior to serum ferritin level for diagnosis of iron deficiency in head-to-head comparisons.

In some cases, the clinician may

TABLE 1. INTERPRETATION OF IRON STUDIES

Serological marker	Iron deficiency	Anaemia of chronic inflammation	Iron overload
Ferritin	Low	High	High
Transferrin saturation	Low	Normal/low	High
Iron	Low	Low	High
Transferrin	High	Normal/low	Low

consider a therapeutic trial of iron when the presence of iron deficiency is in doubt. The diagnosis is confirmed by resolution of the anaemia and improved red cell indices. Reticulocytosis may be seen after seven days and the patient's haemoglobin level should increase within four weeks. A lack of response to iron supplementation is not helpful diagnostically and necessitates reconsideration of a bone marrow biopsy.

Anaemia of chronic inflammation (ACI; formerly anaemia of chronic disease) may be difficult to distinguish from IDA, and the two conditions commonly coexist. In ACI, high levels of IL-6 stimulate hepcidin production. The elevated hepcidin impairs absorption of iron and reduces availability of circulating free iron for haematopoiesis. In addition, the high hepcidin level results in a raised serum ferritin level. ACI is also characterised by reduced production of erythropoietin by the kidneys and a reduced bone marrow response to circulating erythropoeitin. These effects and reduced red cell survival all contribute to anaemia. ACI is typically normochromic and normocytic; however, a microcytic and hypochromic picture may occur, particularly when iron deficiency is coexisting.

Diagnostic workup

The diagnostic workup for iron deficiency starts with, and is guided by, a comprehensive history and physical examination. The most common causes of IDA are listed in the Box. The likelihood of finding a sinister underlying cause is, in general, proportional to the age of the patient and the severity of the anaemia. Iron deficiency without anaemia is rarely due to a sinister cause.

In most people with IDA endoscopic evaluation comprising gastroscopy (with small bowel biopsies) and colonoscopy should be undertaken. Gastroscopy identifies the cause of IDA in about a third of patients and colonoscopy in another third. About an eighth of patients have dual pathology.

Urinalysis for haematuria may be useful in evaluating IDA, as 1% of patients with IDA have a renal tract malignancy. A substantial proportion of these patients will have overt haematuria.

In the setting of IDA, FOBT should not be used as an alternative to colonoscopy, and a negative FOBT result should not preclude endoscopic evaluation

Faecal occult blood testing (FOBT) is a useful screening test for colorectal cancer in asymptomatic, average-risk patients. However, in the setting of IDA, FOBT should not be used as an alternative to colonoscopy, and a negative FOBT result should not preclude endoscopic evaluation. Coeliac serological testing is useful in screening for coeliac disease in patients with suggestive symptoms or a family history. However, in the presence of IDA, serology should not replace gastroscopy with duodenal biopsy.

In frail or elderly individuals in whom anaesthetic risk is very high, abdominal CT scanning or colonography are alternatives to colonoscopy and can exclude large lesions or metastatic malignancy. However, the rationale for investigating to identify a potentially malignant condition in this cohort should be considered and discussed with the patient before embarking on investigations. Barium enema is now a largely obsolete investigation since the development of CT colonography.

Iron deficiency anaemia in premenopausal women

The aetiology of iron deficiency can be difficult to determine in premenopausal women. Menstrual losses and increased metabolic demands of pregnancy and breastfeeding are the most common causes of IDA in this cohort. An attempt should be made to quantify menstrual losses. Menorrhagia is experienced by about 30% of women of reproductive age, and self-judgement of menstrual losses can be difficult and unreliable. Coexistent menstrual and gastrointestinal losses occur in up to a third of women. Even when IDA is explained by a history of excessive menstrual blood loss, if iron deficiency persists despite addressing menstrual losses then evaluation of the gastrointestinal tract should be considered.

Iron malabsorption is more common than gastrointestinal bleeding in premenopausal women. Along with correction of iron deficiency, serum tissue transglutaminase (with serum IgA) is a useful screening test in this patient group. However, the presence of gastrointestinal symptoms or other risk factors for gastrointestinal abnormality (such as a family history of bowel cancer) should prompt consideration of endoscopic evaluation.

Obscure and occult gastrointestinal bleeding

Obscure and occult gastrointestinal bleeding is a common and often frustrating problem for patients and clinicians. Occult bleeding refers to gastrointestinal

CAUSES OF IRON DEFICIENCY

Intestinal blood loss

- Gastric/duodenal ulcers
- Angiodysplasia/angioectasia
- Benign and malignant tumours in the gastrointestinal tract
- Cameron erosions associated with large hiatus hernias
- Haemorrhoidal bleeding
- Inflammatory bowel disease
- Hookworm infestation
- Gastric antral vascular ectasia (GAVE, also known as watermelon stomach)
- Portal hypertensive gastropathy associated with cirrhosis or noncirrhotic portal hypertension
- NSAID use and associated enteropathy

Dietary insufficiency

- Vegetarian and vegan diets
- Poor intake of red meat
- Vitamin C deficiency (scurvy)

Malabsorption

- Coeliac disease
- Whipple's disease
- Tropical sprue
- Atrophic gastritis (including pernicious anaemia)
- Small intestinal bowel overgrowth
- Immunodeficiency disorders
- Gastric surgery, including gastric bypass and small bowel resection

Extraintestinal blood loss

- Menorrhagia
- Haemoptysis/epistaxis
- Renal tract bleeding

Increased metabolic requirements

- Pregnancy
- Lactation

bleeding where blood loss is not clinically evident. Gastroduodenal bleeding of up to 150 mL/day for example, will not result in a change in stool colour but will cause iron deficiency over time. Obscure bleeding is defined as gastrointestinal bleeding that is persistent or recurrent, with no source identified despite initial endoscopic evaluation. Obscure bleeding can be occult, or clinically apparent with frank blood or melaena.

Interrogation of the small bowel should be considered in the setting of obscure bleeding. CT enterography has largely replaced small bowel series for radiological assessment of the small bowel. CT enterography has the advantage of being able to detect both intestinal and extraintestinal gastrointestinal causes of IDA (e.g. renal tract malignancies). However, neither small bowel series nor CT enterography is useful for diagnosis of intestinal mucosal vascular abnormalities such as angioectasia (the most common cause of obscure, small bowel bleeding).

Failure to respond to oral iron treatment may be due to noncompliance, malabsorption, incorrect diagnosis, intercurrent disease or ongoing GI blood loss

Wireless capsule endoscopy (WCE) or 'pill cam' is the most sensitive investigation in the setting of recurrent or persistent iron deficiency anaemia or gastrointestinal bleeding when a gastroscopy and colonoscopy has not identified the source. WCE identifies a source of bleeding in about 60 % of patients but is not therapeutic and does not provide a tissue diagnosis. Many of the mucosal lesions identified with WCE are benign and do not require specific therapy.

After a mucosal lesion is identified by WCE, various enteroscopic techniques may be used for evaluation of the small bowel. Enteroscopy is usually reserved for obtaining a tissue diagnosis (if required) or delivery of therapeutic interventions such as treatment of angioectasias. The simplest technique, push enteroscopy, uses a longer endoscope than for conventional gastroscopy and allows visualisation of the entire duodenum and some of the proximal jejunum. Device-assisted forms of enteroscopy, such as balloon enteroscopy, are more specialised procedures with longer procedure times and greater procedure-associated risks. Balloon enteroscopy uses a specialised endoscope with an overtube that incorporates one or two balloons that are inflated and deflated in order to advance the endoscope further into the small bowel. An anterograde or retrograde approach is taken, depending on the site of interest identified on imaging or WCE.

Iron replacement

Effective management of IDA relies on iron replacement in addition to addressing the causative factor. Oral iron replacement is appropriate in most patients. It is cheap, well tolerated by most patients, effective and is available in many forms (Table 2). However, gastrointestinal side effects including constipation and nausea occur in 20 to 40% and contribute to poor adherence to treatment. An adequate dose of oral iron is more than 150 mg of elemental iron per day. Treatment should continue until anaemia has resolved (usually three to six months) and a further six months of therapy may be undertaken to ensure adequate replenishment of body stores. Failure to respond to oral iron treatment may be due to noncompliance, malabsorption, incorrect diagnosis, intercurrent disease (such as renal failure) or ongoing gastrointestinal blood loss. In patients with an adequate response to iron therapy, haemoglobin levels should rise by 20 g/L every three weeks on iron supplementation. All patients should be monitored for recurrence of anaemia or iron deficiency.

There are no high-quality studies demonstrating the superiority of any one formulation of oral iron. The formulations that are subsidised under the PBS in Australia are ferrous fumarate with and without folic acid and ferrous sulfate liquid, which provide appropriate doses in a

bioavailable form. Sustained-release preparations (all the available ferrous sulfate tablets and capsules) may be less effective as they are not available for absorption in the duodenum, which is the primary site for iron absorption. Liquid iron replacement allows divided daily doses but the taste may be a barrier to adherence and it can cause dental staining. Newer nonionic formulations such as iron polymaltose have equivalent efficacy to iron sulfate preparations, but may have better gastrointestinal tolerability and can be taken with food. Currently, they are more expensive than other preparations. There is emerging evidence that alternate-day, low-dose (40 to 80 mg) iron supplementation results in better absorption compared with daily dosing at the currently recommended dose of 150 mg, which raises circulating hepcidin levels to counteract iron absorption. Oral iron should be administered apart from calcium supplements, antacids and food intake to maximise absorption. Concurrent administration of vitamin C can aid absorption.

Intramuscular iron injection is painful and can lead to permanent tattooing. Intramuscular iron is poorly absorbed, and is no more effective and does not replenish iron stores any faster than oral iron supplementation. As a result, there is little place for intramuscular iron replacement in current practice.

Intravenous iron replacement is appropriate for a select group of patients who cannot tolerate oral iron, or who require rapid delivery of iron. A list of currently available intravenous iron formulations is given in Table 3. Unlike the older, high-molecular-weight preparations of intravenous iron, the currently available, low-molecular-weight preparations such as iron sucrose and iron polymaltose are well tolerated, with a low risk of anaphylactic reactions. Iron sucrose is the formulation of choice for patients undergoing dialysis and receiving concurrent erythropoietin stimulating agents, in whom slower infusion times and lower doses are less important.

TABLE 2. ORAL IRON PREPARATIONS AVAILABLE IN AUSTRALIA

Brand name	Formulation/other active ingredients	Elemental iron content
Ferro-grad	• Ferrous sulfate 325 mg • Controlled-release tablets	105 mg
Fefol	• Ferrous sulfate 270 mg • Folic acid 300 mcg • Delayed-release capsules	87 mg
Ferro-grad F	• Ferrous sulfate 250 mg • Folic acid 300 mcg • Modified-release tablets	80 mg
Ferro-grad C	• Ferrous sulfate 325 mg • Vitamin C 500 mg • Modified-release tablets	105 mg
Ferro-tab (PBS subsidised)	• Ferrous fumarate 200 mg • Noncontrolled-release tablets	65.7 mg
Ferro-F-tab (PBS subsidised)	• Ferrous fumarate 310 mg • Folic acid 350 mcg • Noncontrolled-release tablets	100 mg
Maltofer tablets	• Iron polymaltose 370 mg • Noncontrolled-release tablets	100 mg
Ferro-liquid (PBS subsidised)	• Ferrous sulfate 30 mg/mL oral liquid	6 mg/mL
Maltofer oral liquid	• Iron polymaltose 370 mg/10mL oral liquid	10mg/mL

Iron polymaltose has a longer infusion time but is less expensive and has the advantage of being dose adjusted for body weight and sex. Iron polymaltose is the preferred formulation for inpatients when prolonged infusion times are of less significance.

The newest intravenous formulations such as ferric carboxymaltose and ferric derisomaltose have the advantage over other formulations of much shorter infusion times. Ferric carboxymaltose is delivered over 15 minutes at a maximum dose of 1000 mg, which renders it the most practical formulation for use in general practice or an outpatient setting. There is extensive experience of safe use of ferric carboxymaltose in pregnancy, although it does carry a B3 category from the TGA and it is generally advised to avoid IV iron during the first trimester. Ferric derisomaltose was approved for subsidisation under the PBS in February 2019. It can be administered at a dose of up to 1500 mg. Doses of up to 1000 mg can be administered over 20 minutes. Doses exceeding 1000 mg can be administered over 30 minutes. Despite the good safety profile of modern intravenous iron preparations, a small proportion of patients experience anaphylactic reactions and it should therefore be administered in a setting where resuscitation facilities are available.

Blood transfusion is not an appropriate treatment for iron deficiency anaemia, except in rare clinical circumstances, such as patients with end-organ compromise or continued, haemodynamically significant bleeding.

TABLE 3. INTRAVENOUS IRON PREPARATIONS AVAILABLE IN AUSTRALIA

Brand name (formulation)	Dose			Safety in pregnancy	Safety in renal failure	General patient charge on PBS
Ferinject (ferric carboxymaltose)	1000 mg per infusion			B3 Studies report safe use in pregnancy	Yes	$40.30 per 1000 mg
Ferrosig (iron polymaltose)	Adjusted for weight and haemoglobin level			B3 Studies report safe use in pregnancy	Yes	$29.86 per 500 mg
Monofer (ferric derisomaltose)	**Haemoglobin level**	**Dose if body weight 50 to <70 kg**	**Dose if body weight ≥70 kg**	B3 Limited published evidence of safe use in pregnancy.	No	$40.30 per 500 mg
	≥100 g/L	1000 mg	1500 mg			
	<100 g/L	1500 mg	2000 mg			
Venofer (iron sucrose)	500 mg per infusion			B3	Yes – indicated only for patients undergoing haemodialysis	$40.30 per 500 mg

Conclusion

IDA is commonly encountered in primary practice. The diagnosis is usually made by correct interpretation of a full blood count and iron studies. Once the diagnosis is made, a cause should be sought through careful clinical assessment and the deficiency should be corrected, usually with oral iron therapy. Gastrointestinal bleeding is the most common cause of iron deficiency in men and postmenopausal women. In most medically fit patients with iron deficiency anaemia, endoscopic evaluation of the upper and lower gastrointestinal tract with gastroscopy and colonoscopy should be performed. MT

Further reading

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