

# Iron deficiency

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Iron deficiency is one of the leading contributors to the global burden of disease, and particularly affects children, premenopausal women, and people in low-income and middle-income countries. Anaemia is one of many consequences of iron deficiency, and clinical and functional impairments can occur in the absence of anaemia. Iron deprivation from erythroblasts and other tissues occurs when total body stores of iron are low or when inflammation causes withholding of iron from the plasma, particularly through the action of hepcidin, the main regulator of systemic iron homeostasis. Oral iron therapy is the first line of treatment in most cases. Hepcidin upregulation by oral iron supplementation limits the absorption efficiency of high-dose oral iron supplementation, and of oral iron during inflammation. Modern parenteral iron formulations have substantially altered iron treatment and enable rapid, safe total-dose iron replacement. An underlying cause should be sought in all patients presenting with iron deficiency: screening for coeliac disease should be considered routinely, and endoscopic investigation to exclude bleeding gastrointestinal lesions is warranted in men and postmenopausal women presenting with iron deficiency anaemia. Iron supplementation programmes in low-income countries comprise part of the solution to meeting WHO Global Nutrition Targets.

## Introduction

Iron deficiency (ID) and iron deficiency anaemia (IDA) cause an immense disease burden worldwide. Globally, there were over 1.2 billion cases of IDA in 2016.<sup>1</sup> IDA is among the five greatest causes of years lived with disability globally, the leading cause of years lived with disability in low-income and middle-income countries (LMICs), and is the leading cause of years lived with disability among women across 35 countries.<sup>1</sup> Controlling anaemia is a global health priority: WHO is aiming for a 50% reduction in anaemia prevalence in women by 2025.<sup>2</sup>

When iron intake is inadequate to meet requirements or to compensate for physiological or pathological losses, body iron stores become depleted. Absolute ID occurs when iron stores are insufficient to meet the needs of the individual, and is particularly common in young children (younger than 5 years) and premenopausal (especially pregnant) women. In patients with inflammation, withholding of iron from the plasma promotes iron deficient erythropoiesis and anaemia despite adequate body iron stores (functional iron deficiency). This process is common in patients with complex medical or surgical disorders, in people living in areas where infection prevalence is high, and in patients receiving erythropoiesis stimulating agents.<sup>3</sup>

Iron is crucial for numerous physiological and cellular processes, and ID causes diverse health consequences. Management of ID is an important and complex challenge faced by practitioners of medicine, nutrition, and public health worldwide. In this Seminar, we update the physiology, diagnosis, and clinical management of ID and identify future translational and clinical research directions.

## Clinical presentation

ID can cause symptoms both in the presence and absence of anaemia, or can be asymptomatic. Common symptoms and signs include fatigue and lethargy,

reduced concentration, dizziness, tinnitus, pallor, and headache. In susceptible individuals, ID promotes restless leg syndrome.<sup>4</sup> Other presentations include alopecia, dry hair or skin, koilonychia, and atrophic glossitis. Symptoms in infants (aged younger than 12 months) with ID can include poor feeding and irritability.<sup>5</sup> Patients might also present with pica: the compulsive ingestion of non-nutritive foods, such as soil or clay, ice, or raw ingredients (eg, uncooked rice).<sup>6</sup> ID and anaemia can also exacerbate symptoms and worsen the prognosis of medical conditions, including heart failure<sup>7</sup> and ischaemic heart disease.<sup>8</sup> Severe IDA can cause haemodynamic instability. Preoperative anaemia increases the risk of blood transfusion and is correlated with postoperative morbidity and mortality.<sup>9</sup> Even when asymptomatic, ID can promote suboptimal functional

### Search strategy and selection criteria

We searched MEDLINE, Embase, and the Cochrane Register, with combinations of the search terms including ("iron" OR "iron deficiency" OR "iron deficiency an[a]emia" OR "an[a]emia" OR "supplementation" OR "ferrous" OR "ferric" OR "ferric carboxymaltose" OR "iron carboxymaltose" OR "iron isomaltoside" OR "ferric derisomaltoside" OR "ferumoxytol" OR "iron sucrose" OR "iron polymaltose" OR "iron dextran" OR "nutrition" OR "iron absorption" OR "c[eliac disease]" OR "ferritin" OR "hepcidin" OR "ferroportin" OR "erythroferrone") AND ("public health" OR "epidemiology" OR "systematic review" OR "meta-analysis" OR "randomis[ed] controlled trial"). We searched from database inception until Dec 23, 2019. We also searched the reference lists of articles identified by this search strategy and selected the articles that we judged relevant. Where multiple sources of evidence were available for the same topic, we prioritised evidence from the most recently available systematic reviews or, where unavailable, studies using a randomised controlled trial design.

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outcomes, including impaired physical exercise performance, child neurocognitive development, and pregnancy outcomes.<sup>10</sup>

### Epidemiology of ID

In 2016, 41·7% of children (younger than 5 years), 40·1% of pregnant women, and 32·5% of non-pregnant women were anaemic worldwide.<sup>11,12</sup> WHO estimates that 42% of anaemia cases in children and 50% in women are amenable to iron supplementation, with variation between regions.<sup>13</sup> Meta-analyses of population studies suggest the contribution of ID to anaemia could be smaller than the WHO estimate: 25% in children and 37% in women.<sup>14</sup> Because of the paucity of population studies measuring iron biomarkers (beyond haemoglobin) and complexities in their interpretation during inflammation, prevalence estimates of ID in LMICs are uncertain. Representative population studies are possible: for example, the prevalence of ID in children aged 6 months to 5 years was estimated at 20·2% in Cameroon, 10·6% in Colombia, 18·4% in Laos, 26·1% in Liberia, and 14·8% in Mexico; in the same countries, the adjusted prevalence of ID in non-pregnant premenopausal women was 13·7%, 24·1%, 24·0%, 19·9%, and 30·4%, respectively.<sup>15</sup> In the USA, 11% of children aged 6 months to 5 years, 15% of premenopausal women,<sup>15</sup> and 18% of pregnant women<sup>16</sup> have been estimated to have ID. ID and anaemia are more common in disadvantaged subpopulations, including people on low incomes, Indigenous peoples,<sup>17</sup> and refugees and migrants from LMICs.<sup>18</sup>

### Molecular pathology of ID

Most body iron is contained in haemoglobin found in erythrocytes (2500 mg), and much of the remaining iron is contained in myoglobin (130 mg) and enzymes (150 mg), with surplus iron stored in the liver; average iron stores the US population are 9·7 mg/kg in men, 5·7 mg/kg in premenopausal women, and 7·8 mg/kg in postmenopausal women.<sup>19</sup> The 0·1% of total body iron contained in plasma is bound to transferrin, and in this form, iron can be supplied to tissues via binding to the transferrin receptor. At the cellular level, iron is crucial for numerous functions, including DNA synthesis and repair, enzymatic activity, mitochondrial function, and neurotransmitter production and function.<sup>20</sup> Plasma iron is rapidly turned over, and is predominantly sourced from iron scavenged from senescent red blood cells by macrophages, with a smaller amount (1–2 mg per day) absorbed from the diet at the duodenum, in which body iron acquisition is homeostatically regulated.<sup>6</sup>

Hepcidin, a liver-derived hormone, is the central regulator of systemic iron homeostasis (figure 1). Hepcidin binds to ferroportin, a protein that exports cellular iron, to block iron efflux by both occluding the channel and by inducing degradation of iron-loaded ferroportin.<sup>21,22</sup> Inhibition of ferroportin-mediated iron efflux limits iron

export to the plasma, especially from macrophages and duodenal enterocytes, as well as hepatocytes. In response to both iron load and innate immune signalling, hepcidin is upregulated by the BMP/SMAD pathway and the IL-6-STAT3 pathway, respectively.<sup>20</sup> During absolute ID or periods of increased iron demand, hepcidin suppression upregulates iron absorption and recycling to optimise iron supply. During inflammation, increased concentrations of hepcidin and reduced ferroportin transcription<sup>23</sup> limits iron supply to the plasma, causing functional ID.

Reduced iron availability for red blood cell production causes iron deficient erythropoiesis manifesting as hypochromia, microcytosis, and eventually, anaemia. IDA affects erythropoiesis by influencing renal erythropoietin production and by modulating erythroblast EPO sensitivity, via TFR2.<sup>24</sup> In absolute ID, erythroblasts and erythrocytes donate iron via ferroportin, and can buffer plasma iron levels to mitigate serum iron depletion and protect erythrocytes from oxidative stress.<sup>25,26</sup> These data reframe the assumption that microcytic anaemia is the main end-organ dysfunction from absolute ID; rather, erythroid cells release iron to maintain iron supply elsewhere.

### Clinical pathophysiology of absolute ID

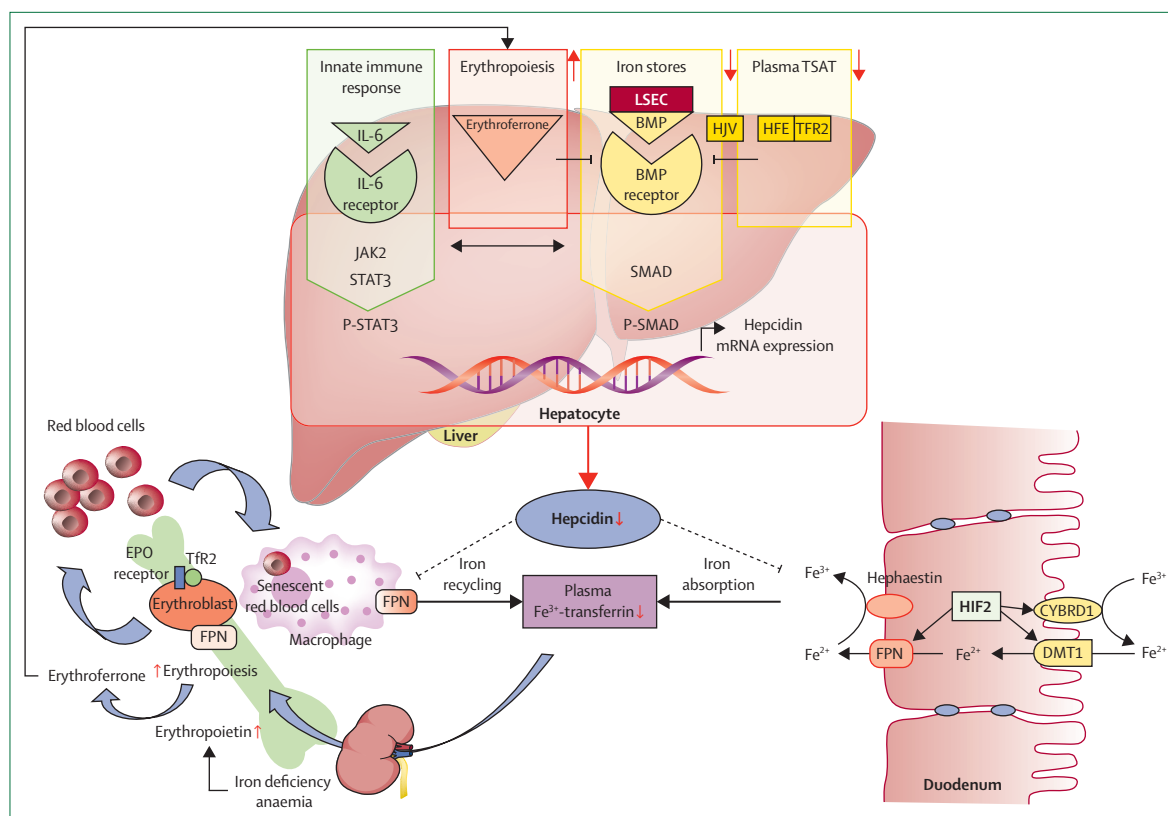
The main causes of absolute ID are excessive blood loss, and inadequate dietary iron intake or absorption that fails to meet physiological requirements (panel 1).

#### Blood loss

Each mL of blood contains 0·4–0·5 mg of iron.<sup>27</sup> Hence, negative iron balance is promoted by physiological, pathological, or iatrogenic blood losses.

Iron stores in premenopausal women are more greatly influenced by menstrual blood loss volume than dietary iron intake.<sup>28</sup> Heavy menstrual bleeding affects about 20% of women,<sup>29</sup> and ID affects around 50% of such cases in referral populations.<sup>30</sup> Up to 20% of women with heavy menstrual bleeding complicated by IDA have an underlying bleeding disorder (most often, von Willebrand disease).<sup>31</sup>

Gastrointestinal blood loss is the most important cause of ID in men and postmenopausal women. Gastrointestinal bleeding can be occult, in which case ID or IDA could be the only evidence of luminal pathology. Common upper gastrointestinal causes of bleeding include erosions or ulcers related to aspirin and other non-steroidal anti-inflammatory drugs, and peptic ulcer disease.<sup>32,33</sup> The most important occult causes of lower gastrointestinal bleeding are colorectal cancer, angiodysplasia, and colonic polyps.<sup>32,33</sup> In patients with IDA referred for endoscopy, potentially bleeding lesions were seen in 62%, including colorectal cancer in 11% and peptic ulceration in 19%.<sup>32</sup> Even in male individuals younger than 50 years with IDA, colon cancer was seen in 0·8%.<sup>34</sup> A population study showed that, in the 2 years after a diagnosis of IDA and ID, the risk of gastrointestinal



**Figure 1: Coordinated homeostatic response to absolute and functional iron deficiency**

Red arrows refer to physiological stimuli (eg, absolute iron deficiency or increased erythropoiesis) that suppress hepcidin expression. During absolute iron deficiency, decreased circulating transferrin saturation and liver iron storage suppress hepcidin transcription via reduced BMP-SMAD signalling (yellow pathway). As a consequence, duodenal and macrophage FPN proteins are stabilised, facilitating dietary iron absorption in duodenal enterocytes and release of iron from macrophages of the reticuloendothelial system, thereby increasing iron concentrations in the plasma. Additionally, reduced iron concentration in duodenal enterocytes is sensed by the iron-dependent prolyl hydroxylase domain enzymes that increase stability of the transcription factor HIF-2, which regulates transcription of apical (CYBRD1 and DMT1) and basolateral (FPN) iron transport machinery. During iron deficiency, in most cell types the IRP/IRE system stabilises mRNAs of proteins crucial for iron uptake (eg, TFR1 and DMT1) and suppresses the synthesis of proteins involved in the storage (ferritin), utilisation (cytoplasmic and mitochondrial iron-containing proteins), and export (FPN) of iron. In functional iron deficiency, inflammation increases hepatic hepcidin expression via IL6-JAK2-STAT3 signalling (green pathway), causing reduced FPN abundance and function on cells, depriving the plasma of iron. In response to iron deficiency anaemia, the kidney produces erythropoietin, which stimulates erythropoiesis. Erythroblast erythropoietin sensitivity can be modulated by TFR2. In absolute iron deficiency, erythroblasts and erythrocytes donate iron through FPN-mediated iron export. Increased erythropoiesis (eg, during recovery from anaemia) causes secretion of erythroferrone, which suppresses hepatic hepcidin expression via inhibition of BMP-SMAD signalling (red pathway). LSEC=liver sinusoidal endothelial cell. P=phosphorylated. TSAT=transferrin saturation.

malignancy is 6% in men and 1% in postmenopausal women, compared with 0.2% in non-anaemic, non-ID controls.<sup>35</sup> Contrastingly, in premenopausal women, no cases of cancer were diagnosed after IDA or ID. Other causes of gastrointestinal blood loss include inflammatory bowel disease; for example, 29% of patients with Crohn's disease and 17% with ulcerative colitis are anaemic,<sup>36</sup> with over 50% of such cases due to ID.<sup>37</sup> In LMICs, chronic hookworm infection promotes gastrointestinal blood loss, with the severity of ID proportional to the worm burden.<sup>38</sup>

Each whole blood donation costs the donor about 250 mg of iron;<sup>39</sup> thus, whole blood donors have an increased risk of ID, with donation frequency being the predominant risk factor. A 2017 trial randomly assigned 45 263 whole blood donors to different inter-donation intervals; the prevalence of anaemia and ID at the shortest interval was 18% and 24% in men and 19%

and 27% in women, respectively, compared with 10% and 12% in men and 16% and 22% in women at the longest interval.<sup>4</sup> Apheresis donation, in which red blood cells are returned to the donor, does not exacerbate ID.<sup>40</sup> Strategies to minimise ID in donors include predonation measurement of ferritin,<sup>41</sup> prolonging the inter-donation interval, and providing postdonation iron supplementation.<sup>42</sup>

#### Inadequate iron intake and absorption

The recommended daily intake for iron is highest in infants aged 7–12 months (11 mg), premenopausal women (18 mg), and during pregnancy (27 mg), and is lowest in adult men (8 mg).<sup>43</sup> Dietary iron occurs as haem iron in meat and non-haem iron from plant sources. Haem iron is efficiently absorbed and less susceptible to modulation by other dietary components, whereas absorption of non-haem iron is less efficient and susceptible to influence; for example, vitamin C enhances non-haem

**Panel 1: Causes of absolute iron deficiency****Inadequate iron uptake**

- Inadequate nutritional iron intake
  - Inadequate dietary iron content
    - Low haem iron content (eg, from a vegetarian or vegan diet)
    - Food insecurity or low dietary diversity\* (eg, resulting from poverty, especially in low-income countries)
    - Low iron content complementary diet\* (eg, prolonged breastfeeding, or milk preference)
- Inadequate nutritional iron absorption
  - Concomitant consumption of inhibitors of iron absorption (eg, calcium or tea)
  - Inadequate stomach acidification
    - Atrophic gastritis
    - Use of antacids or proton pump inhibitors\*
    - *Helicobacter pylori* infection
    - Procedures after gastric bypass
  - Intestinal mucosal dysfunction (eg, coeliac disease\* or inflammatory bowel disease)
  - Obesity
  - Inappropriately increased hepcidin concentrations preventing iron absorption (eg, during chronic inflammation or iron-refractory iron deficiency anaemia caused by *TMPRSS6* mutations)

**Increased iron requirements**

- Growth (eg, during early childhood and adolescence)\*
- Pregnancy\*
- Physiological blood losses exceeding iron intake\*
- Erythropoiesis stimulating agent therapy\*

**Blood loss**

- Intestinal blood loss
  - Oesophageal
    - Varices
    - Carcinoma
    - Ulceration
    - Reflux oesophagitis
  - Gastric\*
    - Gastric cancer and gastric polyps\*
    - Gastric ulcers\*
    - Use of aspirin and other non-steroidal anti-inflammatory drugs\*
    - Angiodysplasia, telangiectasia, and gastric antral vascular ectasia (watermelon stomach)
  - Small bowel
    - Hookworm (*Ancylostoma duodenale* and *Necator americanus*)\*
    - Inflammatory bowel disease\*
    - Duodenal ulcers

- Lymphoma, cancer, and polyps
- Angiodysplasia, telangiectasia, and Meckel's diverticulum
- Extreme exercise-induced gastrointestinal bleeding
- Milk protein allergy (in infants younger than 12 months)
- Colon
  - Colon cancer\*
  - Polyps\*
  - Diverticular bleeding\*
  - Angiodysplasia\*
  - Inflammatory bowel disease\*
  - Heyde's syndrome (severe aortic stenosis, acquired type 2 von Willebrand syndrome, angiodysplasia, and iron deficiency anaemia)
  - Hamartomatous polyps in Peutz-Jeghers syndrome
- Anal
  - Haemorrhoids
- Entire gastrointestinal tract
  - Hereditary haemorrhagic telangiectasia
- Gynaecological bleeding
  - Menstrual (eg, in premenopausal women and girls)\*
  - Exacerbated by bleeding disorders (von Willebrand disease\*, carrier for haemophilia A or B, and platelet dysfunction)
  - Use of an intrauterine device
  - Fibroids
  - Uterine or other reproductive tract cancers
- Urinary tract bleeding
  - Renal or bladder cancer
  - Urinary schistosomiasis (*Schistosoma haematobium*)
  - Intravascular haemolysis (eg, paroxysmal nocturnal haemoglobinuria)
  - Intravascular haemolysis (eg, valve haemolysis, march haemoglobinuria, and malaria)
- Respiratory bleeding
  - Severe haemoptysis (eg, lung cancer and infection)
- Blood donation (especially whole blood donation\*)
- Excess iatrogenic blood losses (eg, excessive blood collection for diagnostic testing and iron losses during haemodialysis)
- Self-inflicted blood loss (Munchausen syndrome)

**Exercise**

- Multifactorial: reduced dietary iron intake, reduced iron absorption due to inflammation, increased losses in sweat, gastrointestinal bleeding, and haemolysis with haemoglobinuria

\*Common important causes to consider in primary care.

iron absorption, and phytates (found in seeds and grains), calcium, and tannins (found in tea and coffee) inhibit non-haem iron absorption.<sup>44</sup> Iron absorption from vegetarian diets is less efficient than meat inclusive diets,

and vegetarians have lower iron stores and are more likely to be iron deficient.<sup>45</sup> A systematic review showed that adult vegetarians have reduced serum ferritin levels compared with non-vegetarians ( $-29.7 \mu\text{g/L}$  in vegetarians

[95% CI -39.7 to -19.7]), with the effects more pronounced in men (-61.9 µg/L [-85.6 to -38.2]) than in women (-13.5 µg/L [-23.0 to -4.0]).<sup>45</sup>

Gastric acidity is crucial for maintaining iron solubility in the duodenum for absorption. Patients using proton pump inhibitors or histamine-2 receptor antagonists are at a dose-dependent and duration-dependent increased risk of ID.<sup>46</sup> ID develops in 20% of patients after gastrectomy (for cancer) or gastric bypass surgery (for obesity). Autoimmune gastritis, an inflammatory condition characterised by autoantibodies against gastric parietal cells and intrinsic factor, causes cobalamin deficiency and megaloblastic anaemia and was reported in 27% of patients with otherwise unexplained IDA.<sup>47</sup> *Helicobacter pylori* was estimated to have infected 4.4 billion people worldwide in 2015, with the prevalence highest in poorest populations.<sup>48</sup> A meta-analysis reported an association between *H. pylori* and IDA and ID, and evidence that eradication could improve iron stores.<sup>49</sup>

Coeliac disease is a chronic small intestinal immune-mediated enteropathy precipitated in genetically predisposed individuals by exposure to dietary gluten, a protein in wheat, barley, and rye.<sup>50,51</sup> Strict removal of dietary gluten promotes mucosal healing. The global seroprevalence is 1.4% and the prevalence confirmed by biopsy is 0.7%.<sup>52</sup> ID and IDA in coeliac disease can occur in the absence of other malabsorptive manifestations and might be the presenting feature. One in 31 patients with IDA could have coeliac disease,<sup>53</sup> with this risk unaffected by sex, age, or prevalence of coeliac disease in the underlying population, indicating coeliac disease is a consistent risk factor for IDA.

Iron absorption in women who are overweight and obese is lower than in women in the healthy weight range<sup>54</sup> due to increased hepcidin concentrations.<sup>55</sup> A systematic review showed that, compared with people who were a healthy weight, individuals who were overweight and obese had lower transferrin saturation (-2.34% [95% CI -3.29 to -1.40]) and a higher risk of developing ID (odds ratio [OR] 1.31 [1.01-1.68]).<sup>56</sup>

Patients with mutations in the *TMPRSS6* gene have iron-refractory IDA, a rare autosomal recessive disease hallmarked by the inability to absorb dietary iron due to increased hepcidin concentrations that block iron release from macrophages and duodenal enterocytes.<sup>57</sup> Genome-wide association studies have showed that, in the general population, *TMPRSS6* polymorphisms influence haemoglobin concentration, red blood cell size, and iron stores,<sup>58</sup> which implies a genetic susceptibility to ID.

Absolute and functional ID can exist independently or in combination to cause anaemia (figure 2). Systemic inflammation increases hepcidin concentrations, which impairs iron absorption. For example, women in Côte d'Ivoire with asymptomatic *Plasmodium falciparum* parasitaemia showed improved iron absorption after receiving antimalarials.<sup>59</sup> In The Gambia, chronic low

levels of systemic inflammation in young children (aged 6-23 months) have been shown to increase hepcidin concentrations and impair iron absorption, potentially contributing to IDA prevalence.<sup>60</sup> Patients with chronic inflammatory conditions can experience similar pathophysiology.<sup>61</sup>

### Increased iron needs during life

For the first 6 months of life, babies predominantly meet iron needs from their birth iron endowment,<sup>62</sup> which is influenced by birthweight, gestation duration, and the timing of cord clamping. Babies who are preterm, small for their gestational age, and of low birthweight have lower iron stores<sup>63</sup> and are at an increased risk of ID. Delaying cord clamping for 1-3 min allows neonates to maximally retain red blood cells.<sup>64</sup> During the second 6 months of life, iron stores are influenced by birth endowments, by use from growth,<sup>65</sup> and by nutritional iron content.<sup>66</sup>

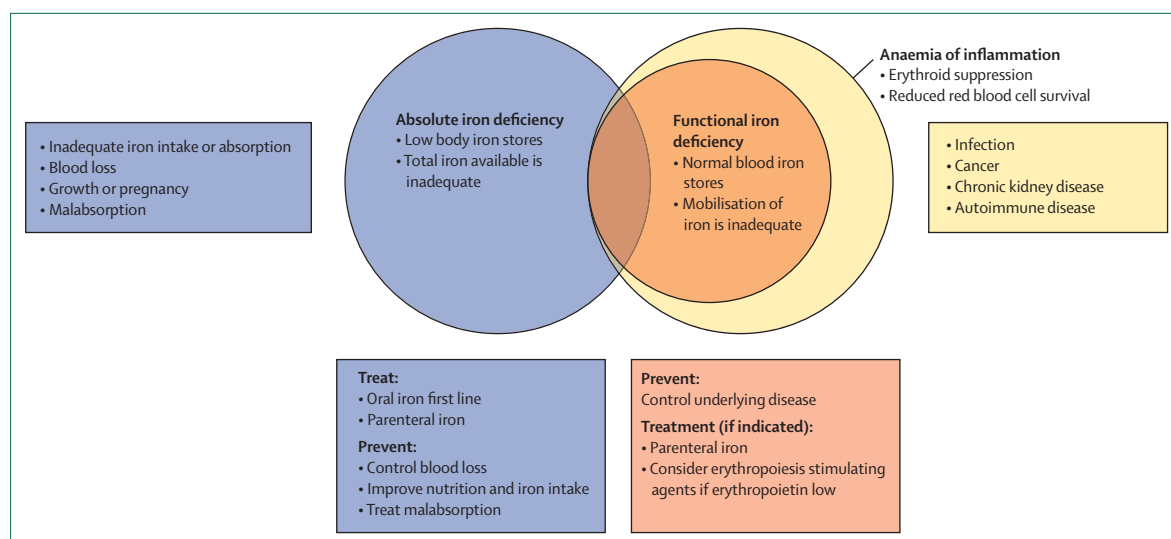
During pregnancy, iron needs markedly increase from the second trimester<sup>67</sup> to support the 30% expansion of the red blood cell mass (which requires about 450 mg iron in a woman weighing 55 kg), although plasma volume expansion promotes physiological anaemia with a haemoglobin concentration nadir mid-second trimester.<sup>68</sup> Furthermore, the fetus requires about 270 mg iron, which is mostly accreted in the third trimester. During childbirth, about 150 mg iron is lost from bleeding. To meet needs, intestinal iron absorption increases as much as nine times from early to late pregnancy, normalising in the postpartum period.<sup>69</sup> This increased iron absorption is accomplished because of hepcidin suppression early in the second trimester.<sup>70</sup> Hepcidin suppression is also crucial for placental iron transfer during the third trimester.<sup>71</sup> Recycling of iron from the expanded red blood cell pool after pregnancy together with amenorrhoea reduces the net pregnancy iron requirement to about 580 mg.<sup>67</sup> Despite homeostatic compensations, many women are unable to meet their pregnancy iron requirements, especially if they enter pregnancy with diminished stores.

ID affects up to 35% of female individuals and 11% of male individuals who are elite (especially endurance) athletes. The pathophysiology is multifactorial and includes interactions between impaired nutritional iron absorption due to inflammation, exercise-induced gastrointestinal bleeding, heavy menstrual bleeding, iron losses in sweat, and increased requirements for erythropoiesis.<sup>72,73</sup>

### Diagnosis of ID

The gold standard test for absolute ID is the finding of absent stainable bone marrow iron. Patients with functional ID have detectable stainable bone marrow iron unless they have concomitant absolute ID (figure 2). Bone marrow aspiration is invasive and rarely done routinely for diagnosis of ID, but it remains useful in complex cases. ID is usually diagnosed by blood biomarkers (figure 3). A full





**Figure 2: Absolute and functional iron deficiency**

In absolute iron deficiency, total body iron concentrations are reduced due to uncompensated negative iron balance. Patients with absolute iron deficiency have low tissue iron stores, low bone marrow iron stores, and low plasma iron (transferrin saturation), and in the absence of other signals, hepcidin is suppressed, homeostatically upregulating iron absorption. Anaemia of inflammation is common in patients with conditions including acute and chronic infection, autoimmune conditions, cancer, recent surgery, and heart failure. The predominant mechanism of anaemia of inflammation is functional iron deficiency, in which inflammation-mediated increases in hepcidin prevent cellular iron export (especially from macrophages) to the plasma, resulting in reduced transferrin saturation, iron deficient erythropoiesis, and anaemia, even with sufficient body iron stores. Functional iron deficiency is the predominant mechanism of anaemia of inflammation, but other causes (eg, direct bone marrow suppression, reduced erythropoietin production and marrow responsiveness, and reduced red blood cell survival) can also contribute. Functional and absolute iron deficiency can coexist, and functional iron deficiency might promote absolute iron deficiency through sustained impairment of iron uptake. Therapy for absolute iron deficiency focuses on improving iron stores, ameliorating blood losses, and optimising iron absorption. Therapy for functional iron deficiency focuses on controlling the underlying conditions. Parenteral iron therapy can be used if the patient is symptomatically anaemic.

blood count with film can indicate anaemia, microcytic, hypochromic red blood cells with an increased red blood cell distribution width (anisocytosis), and elongated (pencil shaped) cells.

Serum (or plasma) ferritin is the mainstay for ID diagnosis.<sup>74</sup> Little primary evidence is available from high quality studies to justify specific thresholds. In a study of 238 healthy women, a ferritin threshold of less than 15 µg/L predicted absent bone marrow iron stores with a sensitivity of 75% and specificity of 98%, and a threshold of 30 µg/L improved sensitivity to 93% at the expense of specificity (75%).<sup>75</sup> Less than 15 µg/L ferritin is specific for ID,<sup>76</sup> whereas less than 30 µg/L ferritin coupled with a high pretest probability is highly suggestive. Use of lower ferritin thresholds for ID diagnosis in children (eg, less than 12 µg/L) or different thresholds between women and men is not evidence-based. Because ferritin is a positive acute phase protein, diagnosis of ID can be obscured by inflammation.<sup>77,78</sup> Strategies for adjusting ferritin concentrations in inflammation include developing a regression equation on the basis of the correlation between ferritin and inflammatory markers, or in the presence of inflammation, inflating the ferritin threshold.<sup>79</sup> When inflammation is present, WHO defines ID at a ferritin concentration less than 30 µg/L in children under 5 years and less than 70 µg/L in older children and adults.<sup>76</sup> Diagnosing absolute ID in patients with inflammation is important for identifying

underlying factors (such as bleeding) and for population estimates of ID; however, treatment approaches should consider coexistent functional ID (figure 2). As with inflammation, ferritin concentrations are also increased in liver disease, including non-alcoholic fatty liver disease, and epidemiological data suggest that population ferritin concentrations are increasing with increasing rates of obesity.<sup>80</sup>

Serum iron concentration is reduced in both ID and inflammation; alone its concentrations do not indicate ID. Transferrin saturation (eg, less than 20%) is useful to define low plasma iron availability to tissues in both absolute and functional ID. Soluble transferrin receptor (sTfR) is a useful index of tissue iron needs, and the sTfR:log(ferritin) ratio has useful predictive value for bone marrow iron stores, especially in patients with inflammation.<sup>81</sup> sTfR is also a biomarker of erythropoiesis. Its drawback is scarce clinical availability and different thresholds between assays due to the fact that different sTfR tests have not been formally standardised.

Reticulocyte haemoglobin content, hypochromic red blood cell percentage, and related indices can be measured on several modern automated haematology analysers. The percentage of hypochromic red blood cells reflects iron restricted erythropoiesis during the preceding 2–3 months.<sup>82</sup> Reticulocyte haemoglobin content reflects iron availability for erythropoiesis of the

	Iron repletion	Low iron stores	Absolute iron deficiency (non-anaemic)	Absolute iron deficiency (anaemia)	Functional iron deficiency	Functional iron deficiency with absolute iron deficiency	Iron-refractory iron deficiency anaemia due to <i>TMPRSS6</i> variants
Body iron stores	Body iron stores and iron available for erythropoiesis				Body iron stores		
					Iron available for erythropoiesis		Body iron stores and iron available for erythropoiesis
No systemic inflammation					Systemic inflammation		No systemic inflammation
Symptoms	Nil	Asymptomatic or mildly symptomatic (eg, fatigue); possible reduced physical or cognitive function; underlying condition could be evident (eg, bleeding or nutrition)	Asymptomatic or symptomatic: fatigue, poor concentration, dizziness, tinnitus, headache, pica, or restless legs	Likely symptomatic, decompensation if severe or poor medical reserves	Symptoms of underlying condition; symptoms of anaemia	Symptoms of underlying condition; symptoms of anaemia	Symptomatic iron deficiency anaemia
Haemoglobin	Normal	Normal	Normal or low-normal	Reduced (anaemic)	Mild to moderate anaemia	Mild to moderate anaemia	Reduced (anaemic)
Mean cell volume and mean cell haemoglobin concentration	Normal	Normal	Normal or reduced	Reduced	Normal or mild reduction	Reduced	Reduced
Ferritin	>30–60 µg/L	15–30 µg/L	<15–30 µg/L	<15–30 µg/L	Normal or increased depending on inflammation and body iron stores	<70–100 µg/L depending on degree of inflammation	Typically 20–50 µg/L
Transferrin saturation	>20%	Usually >20%	<20%	<15%	Usually <20%	<20%	<20%, usually <5%
Reticulocyte haemoglobin content*	Normal	Normal	Low	Low	Low	Low	Low
Soluble transferrin receptor*	Normal	Normal	Increased	Increased	Normal	Normal or increased	Increased
Hepcidin*	Normal	Low-normal	Low	Very low	Increased relative to transferrin saturation	Normal or reduced	High relative to transferrin saturation
Bone marrow stainable iron	Normal	Detectable or absent	Absent	Absent	Detectable	Absent	Absent or trace

**Figure 3: Biomarkers for diagnosis of iron deficiency**

Suggested interpretation of both widely available and emerging biomarkers to diagnose different iron deficiency syndromes. Concomitant measurement of an inflammatory biomarker (eg, C-reactive protein) is recommended to enable interpretation of ferritin in patients at risk of inflammation. \*Diagnostic thresholds for reticulocyte haemoglobin content vary between type of analyser, and for non-standardised hepcidin and soluble transferrin receptor assays, between manufacturers.

previous 3–4 days before testing.<sup>83</sup> Both parameters are useful for detecting iron restricted erythropoiesis due to absolute or functional ID, or recovery in response to therapy.<sup>84</sup> The use of these novel red blood cell parameters is constrained by the absence of universal clinical decision limits. Finally, an increase in haemoglobin concentration after a trial of iron indicates baseline ID.

Measurement of hepcidin concentration is emerging as a test for ID and for distinguishing absolute from functional ID.<sup>85</sup> Hepcidin concentration has been studied in pregnant and non-pregnant women, in

children, and in patients with rheumatoid arthritis, inflammatory bowel disease, cancer-related anaemia, or critical illness.<sup>86–88</sup> Suppressed concentrations indicate physiological iron need, predict responsiveness to iron, and can enable personalisation of the route of iron replenishment.<sup>89</sup> Measurement of hepcidin is mostly limited to research settings but is offered clinically by some European hospital laboratories. The use of calibration materials commutable with human plasma or serum will allow standardisation that is essential to enable routine clinical hepcidin testing.<sup>90</sup>

### Further investigation of ID

ID is the presenting manifestation of various pathophysiological processes, and investigation to exclude serious pathology and define the underlying cause is essential. The nature and extent of testing depends on the patient demographic (appendix p 1).

See Online for appendix

Coeliac serological testing should be considered in patients with non-anaemic ID and is recommended for all patients with IDA.<sup>33,91</sup> Measurement of tissue transglutaminase IgA antibodies is the preferred test, and should be combined with IgA concentrations or an IgG-based assay, such as DGP, because 2–3% of patients with coeliac disease are IgA deficient. Anti-endomysial antibodies are highly specific for coeliac disease. If serological tests are positive, coeliac disease should be confirmed by small intestinal evaluation.<sup>91</sup>

Men and postmenopausal women with IDA are at high risk of bleeding gastrointestinal lesions and should be considered for upper and lower gastrointestinal endoscopy.<sup>33,92</sup> A decision to defer endoscopic investigation in patients with identifiable non-gastrointestinal blood losses should only be made after careful consideration of risks and benefits. Premenopausal women with IDA should be considered for endoscopy if they have symptoms of gastrointestinal disease (eg, altered bowel habit or overt bleeding), a personal history or a first-degree relative with a history of colorectal cancer, or if they do not have a clear explanation for ID, such as ongoing menstrual blood loss.<sup>33</sup> The diagnostic yield from endoscopic procedures in the asymptomatic premenopausal patient population is unclear.<sup>92</sup> Faecal occult blood testing should not be used to target endoscopy in patients with ID. CT colonography can be considered when colonoscopy is contraindicated but does not have the sensitivity for smaller mucosal lesions (less than 6 mm) and does not permit biopsy or polypectomy. Endoscopy is not recommended as routine in patients with non-anaemic ID unless there are other concerns for gastrointestinal malignancy, or if ID is recurrent.<sup>33</sup>

If upper and lower endoscopic studies exclude substantial pathology, it is reasonable to withhold further gastrointestinal investigation unless there is recurrent, refractory, or severe IDA.<sup>33</sup> Small intestinal investigation can be accomplished by video capsule endoscopy (a non-invasive imaging approach) or enteroscopy (an endoscopic approach enabling tissue sampling and therapeutic manoeuvres). Finally, assessment for autoimmune gastritis and *H pylori* should be considered in all patients with ID or IDA for whom no other underlying cause has been diagnosed.<sup>47</sup>

### Treatment of ID

A holistic approach to clinical management of ID is outlined in the appendix (p 2). The aim of treatment is to replenish iron stores and normalise haemoglobin concentrations if anaemia is present. Indications for therapy in ID include anaemia, symptoms, crucial periods

that risk impaired outcomes (eg, pregnancy or before surgery), and when progression is likely to be due to uncorrected underlying factors; for example, ongoing growth in children, poor iron intake, or blood losses. Most patients with non-anaemic ID who are seen clinically will have presented with symptoms and should be treated, whereas patients who are entirely asymptomatic should probably still receive some intervention to prevent further decline in iron stores.

### Oral iron supplementation

Many oral iron products with varying doses and formulations are available. Oral iron formulations include ferrous salts (eg, ferrous sulphate) as well as other agents, including iron polymaltose. Dosing is based on the elemental iron content (eg, 325 mg ferrous sulphate contains 105 mg elemental iron). The use of ferrous salts for iron therapy is limited by gastrointestinal adverse events. A systematic review of placebo-controlled trials supported that ferrous salts increased gastrointestinal symptoms (OR 2.32 [95% CI 1.74–3.08]); particularly constipation (12%), nausea (11%), and diarrhoea (8%).<sup>93</sup> Gastrointestinal symptoms limit adherence and cause cessation of therapy.<sup>94</sup> Slow-release iron formulations aim to reduce side-effects; however, this type of formulation is not effective in clinical studies.<sup>93</sup>

Historically, doses of elemental iron as high as 100–200 mg per day across two to three divided doses were recommended.<sup>95</sup> However, stable isotope studies have redefined optimal oral regimens. In women who are iron deficient and non-anaemic, elemental iron doses of 60 mg or greater raise the concentration of hepcidin for 24 h, blocking absorption of subsequent doses; as iron doses increase, fractional absorption from subsequent doses declines, such that over a six times increase in dose absolute absorption increases by only three times.<sup>96</sup> When sustained absorption of elemental iron from twice daily, daily, and alternate daily dosing was measured, 33% more iron was absorbed over 14 doses when given alternate daily compared with daily; dividing doses worsened fractional absorption.<sup>97</sup> In women with mild IDA, fractional iron absorption was higher when iron was given on alternate days compared with consecutive days, and higher from 100 mg doses compared with 200 mg doses.<sup>98</sup> This approach to iron therapy was tested in a small randomised controlled trial (RCT) comparing treatment of IDA with alternate day dosing at 120 mg with 60 mg twice daily dosing.<sup>99</sup> Patients receiving twice daily dosing had faster increases in haemoglobin concentration, but patients receiving alternate day dosing had similar increments once they had received the same total amount of iron, and experienced fewer gastrointestinal adverse events. Larger studies will be needed to define the comparative effectiveness of treatment regimens for alternate day dosing. Together, these studies<sup>96–98</sup> suggest optimal regimens of oral iron dosing. High doses of iron, and dividing doses twice or thrice daily, is physiologically



inefficient; instead, iron absorption is most efficient with intermediate doses and on alternate days, and this approach is recommended in patients with mild symptoms, or no or mild anaemia. However, high doses do increase absolute absorption; therefore, higher doses can be considered when iron deficits are severe.

Novel oral therapies are emerging that combine ferric iron with carriers to optimise absorption and reduce adverse gastrointestinal effects. Ferric maltol is approved in Europe and in the USA for treatment of IDA in adults.<sup>100</sup> Sucrosomial iron has been evaluated in IDA in patients with kidney disease, cancer, and inflammatory bowel disease, and during pregnancy.<sup>101</sup> Iron hydroxide adipate tartrate is being trialled for prevention and treatment of IDA in young African children (aged 6–35 months).<sup>102</sup>

### Parenteral iron therapy

New generation parenteral iron preparations have revolutionised therapy for ID. Intravenous preparations comprise an iron core encapsulated in a carbohydrate shell to delay iron release.<sup>103</sup> The maximum single infusion dose depends on the stability of the shell. Iron sucrose has a less stable shell, limiting dosing to about 200 mg per infusion.<sup>103</sup> Ferric carboxymaltose, ferric derisomaltose, and ferumoxytol have stable shells, slowing iron release and allowing higher doses of iron to be delivered in single infusions, thereby minimising the number of clinical contacts.

Safety of parenteral iron is a historical concern, based on experience from obsolete high molecular weight iron dextran formulations. A systematic review of 97 RCTs across various (non-high molecular weight dextran) parenteral formulations showed that parenteral iron was not associated with serious adverse events (relative risk [RR] 1.04 [95% CI 0.93–1.17]),<sup>104</sup> nor were ferric carboxymaltose, iron sucrose, ferric derisomaltose, or ferumoxytol associated with serious infusion reactions; milder reactions, such as urticaria, and delayed effects, including headache and arthralgias, were not uncommon. Nonetheless, regulators still advise that parenteral iron should only be given when equipment and staff for management of hypersensitivity reactions are available, and that patients are monitored for hypersensitivity during infusion and for 30 min thereafter.<sup>105</sup> Parenteral iron formulations are now widely used in outpatient settings and primary care. A systematic review did not identify increased risk of infection from parenteral iron.<sup>104</sup> However, given that iron can promote microbial growth, parenteral iron should be avoided in patients with active sepsis. An underappreciated clinical and medico-legal risk of parenteral iron is skin staining if extravasation occurs, and patients should be counselled of this risk.<sup>106</sup> Purchase price of the new drugs are expensive compared with iron sucrose and oral iron; these costs might be offset by the shorter infusion times and fewer clinic visits needed for total dose replacement.<sup>107</sup>

Ferric carboxymaltose has been available for over a decade, is currently marketed in over 50 countries,<sup>108</sup> and has been tested across a range of clinical indications. A dose of 15–20 mg/kg up to 1000 mg (750 mg in the USA) diluted in 250 mL saline is conventionally administered in a 15 min infusion. Biochemical hypophosphataemia is common after administration of ferric carboxymaltose,<sup>109</sup> and is due to a drug-induced increase in FGF23 concentration that acts on the renal tubules to induce phosphaturia.<sup>110</sup> Hypophosphataemia is generally transient, recovering over 8–10 weeks. Although most cases seem asymptomatic,<sup>111</sup> severe clinical hypophosphataemia has been reported,<sup>112</sup> and patients receiving recurrent doses of ferric carboxymaltose can develop osteomalacia.<sup>113</sup> Routine phosphate measurement and replacement after ferric carboxymaltose is not usually necessary, but clinicians should consider hypophosphataemia in patients presenting with muscle dysfunction or changes in mental state in the weeks after treatment and in patients with bone pain or fractures after recurrent usage.

Ferumoxytol is available in the USA: up to 510 mg iron can be delivered in a single dose, which must be diluted in saline or glucose and given over 15 min.<sup>114</sup> Off-label administration of 1020 mg as a single 30-min infusion has been reported.<sup>115</sup> A trial comparing ferumoxytol with ferric carboxymaltose showed similar adverse event profiles, similar efficacy, and lower risks of hypophosphataemia from ferumoxytol<sup>109</sup> due to blunted increases in FGF23.<sup>110</sup> Ferric derisomaltose is available in Europe and has recently been licensed in the USA and Australia. This treatment enables doses of 1500 mg to be delivered over a 30 min infusion, making it an attractive option in patients who are profoundly iron deficient. Twin RCTs showed that biochemical hypophosphataemia is less common with ferric derisomaltose than ferric carboxymaltose (around 8% vs around 74%).<sup>116</sup> Low molecular weight iron dextran is a cheap iron formulation available in the USA which allows total-dose iron replacement over about 60 min.<sup>117</sup> In Australia and New Zealand, iron polymaltose has long been available as a parenteral formulation, is cheap, and can deliver high doses (up to 2000 mg) over 60–120 min infusions.<sup>118</sup>

In pregnancy, the use of parenteral iron is restricted to the second and third trimesters.<sup>119</sup> Case series have reported safe and efficacious use of parenteral iron in children aged 9 months to 18 years for treatment indications similar to adults.<sup>120</sup>

### Clinical benefits of iron therapy

Oral iron is the first line of treatment in uncomplicated ID, but the threshold for use of parenteral iron in cases of moderate or severe anaemia, severe clinical symptoms, poor response, intolerable adverse effects, or difficult adherence is lowering. Parenteral iron generally promotes superior haemoglobin improvements: for example, a systematic review of 13 RCTs showed parenteral iron produces a 5.3 g/L (95% CI 2.1–7.5) greater increase in

haemoglobin compared with oral iron.<sup>121</sup> Considerations for choosing between oral and parenteral iron are discussed in this Seminar and summarised in the appendix (p 2).

### Iron interventions in patients without complex medical conditions

Iron supplementation inevitably increases haemoglobin and ferritin.<sup>122–125</sup> Clinically, iron in adults with non-anaemic ID reduces self-reported fatigue (standardised mean difference [MD]  $-0.38$  [95% CI  $-0.52$  to  $-0.23$ ]).<sup>126</sup> Trials of iron in asymptomatic (non-fatigued) women with ID have shown that iron does not generally improve fatigue scores, suggesting that iron benefits patients with ID who present symptomatically but not patients with ID who are asymptomatic. Iron can improve exercise performance: a systematic review showed that, in women with ID, oral iron improved maximal exercise performance ( $VO_2$  max by  $2.35$  mL/kg per min [95% CI  $0.82$ – $3.88$ ]) and submaximal performance (heart rate  $4.05$  beats per min lower [0.85–7.25]).<sup>127</sup> Parenteral iron did not improve  $VO_2$  max in elite athletes.<sup>128</sup> A systematic review showed that iron (both oral and parenteral) reduced International Restless Legs Syndrome scores (MD  $-3.55$  [95% CI  $-5.41$  to  $-1.68$ ]).<sup>129</sup> Meta-analyses have shown that iron improves cognitive performance in children aged 5–12 years but evidence is minimal for benefits on cognitive development in children younger than 5 years, and especially in children younger than 2 years.<sup>124,125</sup>

A 2015 Cochrane review evaluating antenatal iron supplementation showed that iron reduced anaemia at term by 70%; in a subgroup analysis in which anaemic participants were not specifically excluded, antenatal iron reduced the risk of low birthweight (RR  $0.82$  [95% CI  $0.72$ – $0.94$ ]) and increased birthweight by  $33.02$  g (95% CI  $3.65$ – $62.38$ ).<sup>123</sup> An RCT in Kenya compared oral iron with placebo in 470 unselected pregnant women and had 100% adherence: babies of mothers randomly assigned to iron were  $150$  g heavier and born on average  $3.4$  days later than those born to mothers receiving placebo. Importantly, benefits on birthweight were unrelated to baseline anaemia status but were only noted in women with initial ID (in whom there was a  $234$  g increase in birthweight of the babies).<sup>130</sup> Systematic reviews summarising RCTs comparing parenteral with oral iron in pregnancy<sup>131,132</sup> each found parenteral iron superior for improvements in haemoglobin (MD  $7.4$  g/L [95% CI  $3.9$ – $11.0$ ]);<sup>132</sup> furthermore, parenteral iron produced a small but significant increase in birthweight (about  $58$  g),<sup>131,132</sup> and could reduce maternal transfusion needs (OR  $0.19$  [95% CI  $0.05$ – $0.78$ ]).<sup>132</sup> Collectively, these data emphasise the crucial importance of screening for, preventing, and treating, ID during pregnancy, affirm the importance of routine oral iron supplementation in settings where the risk of antenatal anaemia is likely high,<sup>133</sup> and establish a role for parenteral iron in women with

moderate or severe IDA beyond the first trimester, especially in the third trimester when fetal iron transfer is highest and delivery (and risk of blood loss) is imminent.<sup>119,134</sup>

In the postpartum period, a systematic review found that, compared with oral iron, women treated with intravenous iron had a haemoglobin concentration  $8.8$  g/L [95% CI  $4.1$ – $13.5$ ] higher, with superiority seen as early as 1 week postinfusion.<sup>135</sup>

### Parenteral iron in patients with complex conditions

Impaired oral iron use in functional ID can be circumvented by parenteral iron. Parenteral iron should be considered in the first line of treatment for functional ID, including for patients with the following complex conditions.

#### Congestive cardiac failure

Anaemia and functional ID are common in patients with chronic systolic heart failure. Single-dose<sup>136</sup> and sustained<sup>137</sup> treatment with ferric carboxymaltose improves exercise capacity and quality of life in patients with chronic New York Heart Association Class II or III systolic heart failure and a serum ferritin concentration less than  $100$  µg/L or a ferritin concentration between  $100$  µg/L and  $299$  µg/L with a transferrin saturation less than 20%. A systematic review showed that patients with heart failure receiving parenteral iron (as ferric carboxymaltose or iron sucrose) showed reduced death and heart failure on hospital admission (OR  $0.47$  [95% CI  $0.32$ – $0.69$ ]), and improved symptoms, 6 min walk test distance, and left ventricular ejection fraction, and reduced N-terminal pro-hormone B-type natriuretic peptide.<sup>138</sup> Conversely, oral iron supplementation does not benefit cardiac endpoints in patients with systolic heart failure.<sup>139</sup> Finally, a multicentre RCT of patients admitted to hospital with acute heart failure and reduced ejection fraction and reduced serum ferritin or transferrin saturation (serum ferritin concentration less than  $100$  µg/L or a ferritin concentration between  $100$  µg/L and  $299$  µg/L with a transferrin saturation less than 20%) reported that ferric carboxymaltose at discharge and 6 weeks after discharge, with maintenance as needed thereafter, reduced heart failure-associated hospital admissions compared with placebo.<sup>140</sup> European Society of Cardiology guidelines recommend that ferric carboxymaltose should be considered in symptomatic patients with low ferritin or transferrin saturation to improve heart failure symptoms, exercise capacity, and quality of life.<sup>141</sup>

#### Inflammatory bowel disease

Parenteral iron is preferred in patients with inflammatory bowel disease and moderate to severe anaemia, with active disease, or for whom oral iron is not tolerated or ineffective. A systematic review showed that parenteral iron was more effective at promoting improvements of

20 g/L or higher in haemoglobin concentration compared with oral iron (OR 1.57 [95% CI 1.13–2.18]), with a lower rate of treatment discontinuation due to adverse events.<sup>142</sup>

### Perioperative optimisation

Preoperative anaemia is associated with increased risk of in-hospital (OR 2.09 [95% CI 1.48–2.95]) and 30-day postoperative (OR 2.20 [1.68–2.88]) mortality, along with other serious adverse events.<sup>143</sup> Preoperative therapy with iron improves haemoglobin concentrations,<sup>144</sup> although effects on transfusion requirements also relate to broader operative and postoperative aspects of blood management for patients. A systematic review suggested that preoperative iron supplementation (oral or intravenous) reduces transfusion (RR 0.47 [95% CI 0.28–0.79]);<sup>143</sup> however, a large RCT of patients with anaemia (but not necessarily with ID) undergoing major abdominal surgery did not find a reduction in transfusion needs from preoperative treatment with ferric carboxymaltose, although hospital readmissions were significantly reduced in the ferric carboxymaltose arm, especially in the first 8 weeks postoperatively.<sup>145</sup> Screening for anaemia and defining the contribution of ID should be undertaken before elective surgery, and IDA should be treated with iron replacement, with the selection of route dependent on the severity of the anaemia, the patient's ability to absorb oral iron, and the time until surgery (parenteral iron is preferred if operation is within 6 weeks from diagnosis of ID).<sup>143,146</sup>

Postoperative anaemia is common due to blood losses during surgery and diagnostic testing, and functional ID, or can be spurious due to intraoperative or postoperative haemodilution. Parenteral iron is superior to placebo<sup>147</sup> and oral iron<sup>148</sup> in restoring haemoglobin concentrations in patients with postoperative anaemia after a variety of procedures, although effects on non-haematological clinical endpoints are uncertain.<sup>149</sup>

### Chronic kidney disease

Compared with oral iron, parenteral iron produces higher haemoglobin concentrations (MD 7.2 g/L [95% CI 0.39–1.05]), increases the likelihood a patient will reach their target haemoglobin concentration (RR 1.71 [95% CI 1.43–2.04]), and reduces the required dose of erythropoiesis stimulating agents in chronic kidney disease.<sup>150</sup> A large RCT (n=2141) showed that, compared with reactive treatment with parenteral iron to keep ferritin above 200 µg/L, administering regular, high doses of intravenous iron (eg, 400 mg iron sucrose monthly, unless ferritin exceeded 700 µg/L) improved mortality and morbidity from cardiovascular events and permitted reduced dosing of erythropoiesis stimulating agents.<sup>151</sup> Because ferric carboxymaltose-induced hypophosphataemia is due to renal losses, it is less common in chronic kidney disease.

An emerging non-parenteral approach for treatment of ID in chronic kidney disease is oral ferric citrate, an

intestinal phosphate binder that can improve iron stores and reduce anaemia (even when therapy with parenteral iron and erythropoietin stimulating agents is suspended) while controlling hyperphosphataemia in patients who are dialysis dependent<sup>152</sup> and those who are non-dialysis dependent.<sup>153</sup>

### Preventing ID in LMICs

At the population level, ID and IDA is an outcome of social, environmental, and nutritional determinants that converge to constrain iron intake, increase iron demands, cause blood loss due to helminth infection, and limit iron absorption and use due to inflammation.<sup>154</sup> WHO recommends population level interventions to prevent ID,<sup>155</sup> including central fortification with iron of staple foods and condiments; home fortification of infant complementary foods with iron and other micronutrients; and daily or weekly iron supplementation during childhood, adolescence, and pregnancy, and in non-pregnant

#### Panel 2: Future research and clinical directions

##### Epidemiology

- Improved data on prevalence of iron deficiency across low-income, middle-income, and high-income countries through routine incorporation of iron biomarkers in population surveys will enable appropriate targeting of public health and clinical interventions

##### Diagnosis

- Rational, evidence-based thresholds for defining iron deficiency using existing biomarkers, such as ferritin and standardised soluble transferrin receptor, and available but underused biomarkers, such as reticulocyte haemoglobin content
- Identification and validation of functional markers of iron deficiency beyond haemoglobin
- Introduction of standardised hepcidin measurement into routine clinical diagnosis through availability on automated laboratory platforms
- Non-invasive faecal and blood-based tools and improved imaging technology to detect luminal pathology, such as malignancy and coeliac disease

##### Treatment

- Further characterisation of the clinical role and safety of parenteral iron across the range of iron deficiency syndromes, clinical disease groups, and demographic populations
- Development of personalised iron supplementation strategies based on genetic loci that are associated with treatment outcomes of iron supplementation
- Clarification of clinical implications and role for screening and treatment of parenteral iron-induced hypophosphataemia
- Characterisation of possible long-term adverse effects of sustained parenteral iron therapy in patients with functional iron deficiency (including chronic kidney disease)
- Introduction of novel therapies for functional iron deficiency that inhibit hepcidin production, directly target hepcidin itself, or prevent its action on ferroportin; or promote erythropoietin production and iron transport
- Improved understanding of the benefits, risks, and optimal approaches for delivering iron to prevent and treat anaemia in children, adolescents, and women in low-income countries

women. Other strategies include deworming and delayed cord clamping to optimise infant iron stores. Infection risk complicates iron interventions in low-income settings, especially in children. Where there is high carriage of pathogenic bacteria, iron could reprofile the intestinal microbiome towards more pathogenic flora, promoting infectious diarrhoea.<sup>156</sup> In malaria-endemic settings, iron could promote malaria infection, probably because of parasite trophism for reticulocytes induced during recovery from anaemia.<sup>157</sup> WHO therefore recommends that iron supplementation should only be given in endemic settings with simultaneous malaria prevention, diagnosis, and treatment interventions.<sup>158</sup>

## Conclusions

Clinicians regularly encounter ID and IDA. Understanding the pathophysiology of absolute and functional ID guides diagnosis, appropriate use of established and emerging treatments, and rational deployment of further investigations. Further research into the biology, epidemiology, diagnosis, and treatment of ID (panel 2) will continue to transform approaches to this common condition.

### Contributors

S-RP drafted the manuscript. All authors undertook the literature search, drafted the manuscript, and prepared the figures. S-RP was responsible for the final editing of the manuscript.

### Declaration of interests

S-RP reports grants from the National Health and Medical Research Council, during the conduct of the study, and is an external advisor and a consultant to the World Health Organization, Australian Red Cross Blood Service, and Merck. DWS reports to be an employee of Radboudumc, which offers hepcidin calibration materials and high quality hepcidin measurements at a fee for service via its [www.hepcidinanalysis.com](http://www.hepcidinanalysis.com) initiative, and personal fees from Silence Therapeutics, outside of the submitted work. MUM reports grants and personal fees from Novartis Pharma, grants and personal fees from Silence Therapeutics, personal fees from Vifor Pharma, personal fees from Merck Selbstmedikation, and personal fees from Slovak Republic Ministry of Health, outside of the submitted work. In addition, MUM has patent 125-12ERF (Therapeutic micro RNA targets in chronic pulmonary diseases issued) and patent MJ/d 201/08 (miQPCR – a method for miRNA quantitation) issued. JT-D declares no competing interests.

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