Iron homeostasis: assessment and treatment in clinical practice

KEY LEARNINGS

Iron deficiency disorders

- Iron deficiency (ID) is the most common nutritional deficiency disorder affecting more than 2 billion people worldwide.
- ID refers to low iron stores that do not meet the body's iron requirements, while iron deficiency anaemia (IDA) arises when there is a lack of sufficient iron to form normal red blood cells.
- As differentiating between the various types of anaemia is often difficult, a thorough interpretation of iron markers, including haemoglobin, serum iron, serum ferritin, transferrin, transferrin saturation and transferrin receptors will direct the correct treatment approach.
- Oral iron supplementation is an effective first-line therapy in managing ID/IDA; however, its efficacy is limited due to the frequent gastrointestinal side effects associated with commonly prescribed supplements, such as ferrous fumarate, ferrous sulphate and iron polymaltose.

Iron bisglycinate

- Iron bisglycinate consists of one ferrous iron molecule attached to two molecules of glycine by a covalent bond.
- Once absorbed into the gastrointestinal mucosa via efficient amino acid uptake pathways, this molecule is easily hydrolysed into individual components and released into the bloodstream.
- Iron bisglycinate has been shown to have similar or greater efficacy than other iron forms at improving haematological parameters across various population groups with ID or IDA, including infants, children, cancer patients, pregnant women and people with malabsorption conditions.

Lactoferrin

- Lactoferrin is an iron-binding protein abundantly expressed in human breast milk and is emerging as an important regulator of iron homeostasis.
- Research indicates lactoferrin has a high affinity for sequestering iron and has the ability to acquire, bind and store iron in a non-toxic, readily available form.
- By virtue of its ability to reduce pro-inflammatory cytokine expression, including interleukin-6 (IL-6), lactoferrin represents a novel treatment option in ID, IDA and anaemia of inflammation.
- A number of clinical trials involving pregnant women, children and cancer patients have demonstrated the safety and effectiveness of lactoferrin in managing various iron deficiency disorders.

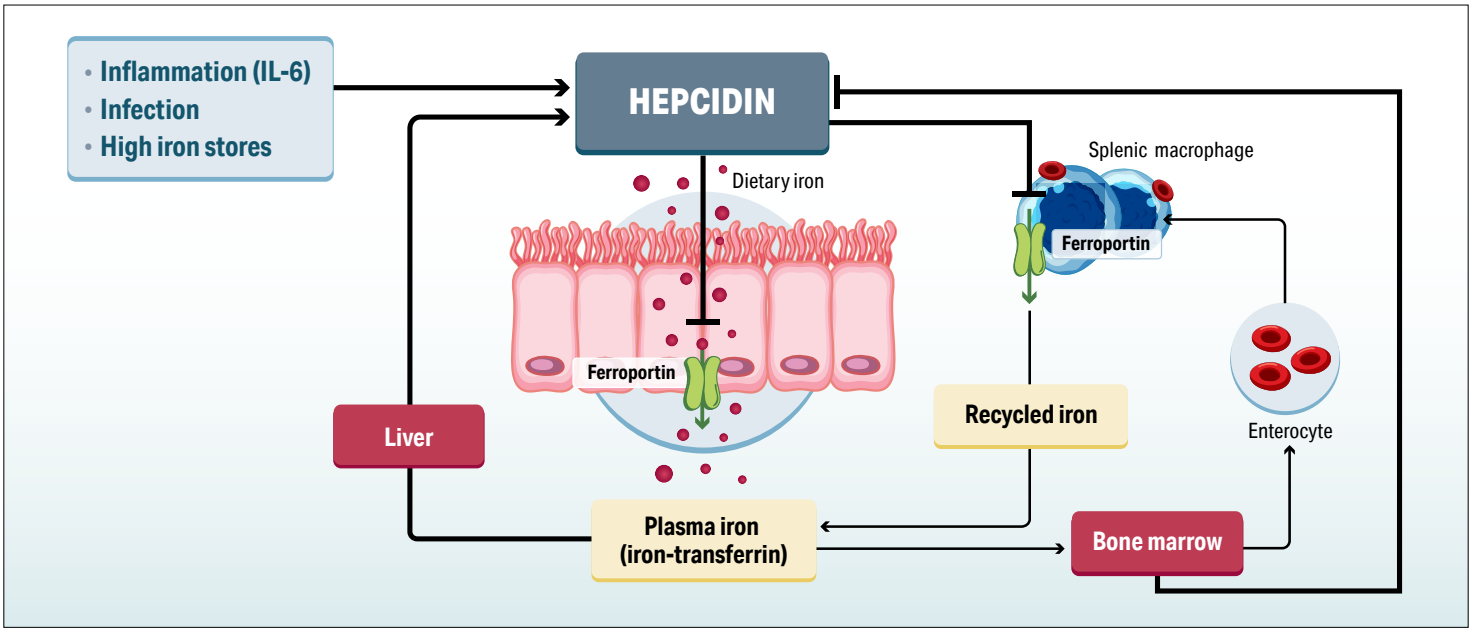
Background

An essential trace element and cofactor for multiple enzymes, iron is involved in various critical physiological processes, such as energy production, oxygen transport, haemoglobin and myoglobin production, neurodevelopment and function, as well as hormone synthesis.[1,2] The human body contains approximately 3–4 grams of iron, with over 65% found in haemoglobin, 10% located in myoglobin, and 1–5% found as a component of enzymes.[3] Iron is primarily bound to transport proteins, predominantly ferritin, transferrin and albumin, leaving only 0.1% of total body iron as free iron in plasma.[4] While iron exists in several oxidative states, ferric (Fe^{3+}) and ferrous (Fe^{2+}) forms are the only states that are stable in the aqueous environment of the body and in food.[3]

Men and non-menstruating women lose approximately 1mg of body iron daily, while menstruating women lose an additional 1mg per day on average.[5] As there is no regulated pathway for the excretion of iron, systemic iron homeostasis is tightly regulated through intestinal iron absorption.[6] The correct balance of iron between tissues and blood is controlled by two main factors, ferroportin and hepcidin.[7] Ferroportin is the only known exporter of iron from cells to blood and is downregulated by high levels of IL-6 and hepcidin.[8] Hepcidin, a circulating peptide hormone, is the key regulator of iron homeostasis and controls the distribution of iron throughout the body by regulating intestinal iron absorption and mobilisation from hepatic stores.[6] With low iron status and in situations of ID, little hepcidin is released, and ferroportin

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Figure 1: Role of hepcidin in iron homeostasis



concentrations remain sufficient, allowing for dietary iron absorption and iron export out of the cells. On the other hand, in cases of iron overload, inflammation or when there are adequate iron stores, hepcidin inhibits dietary iron absorption, promotes cellular iron sequestration and reduces bioavailability.[9] Consequently, high hepcidin concentrations impede the export of iron from cells to blood, while low levels allow iron export via ferroportin (see Figure 1).

Dietary iron sources

Dietary sources include haem iron, primarily found in meat, and non-haem iron, found in plants, dairy products, legumes and fortified foods. Dietary haem iron is relatively unaffected by other dietary and gastrointestinal factors and is absorbed four to five times more easily than non-haem iron.[5,6] In a typical diet, approximately 15mg of dietary iron is consumed per day, of which only 1–2mg is absorbed due to poor bioavailability.[7] While increasing dietary iron may be valuable for preventing ID, it is inadequate to treat IDA.[6]

Iron deficiency disorders

ID, with or without anaemia, is the most common nutritional deficiency disorder, affecting more than 2 billion people worldwide.[10,11] ID refers to low iron stores that do not meet the body's iron requirements and occurs before anaemia develops.[12] IDA arises when there is a lack of sufficient iron to form normal red blood cells and is typically caused by insufficient intake, chronic blood loss, or a combination of both.[13] In contrast, functional iron deficiency exists when despite adequate stores, iron is not utilised for vital body processes due to elevated hepcidin release.[6,12] As the impact of iron deficiency on individuals is extensive, establishing the underlying cause is essential regardless of the severity.[5]

In Australia, approximately 15% of women of child-bearing age and 12% of pregnant women are iron deficient.[5] Anaemia is highly prevalent amongst Australian Indigenous communities, where 52% of school-aged children,[14] 55% of women and 18% of men[15] are reported to be anaemic. While few studies have informed the prevalence of ID or IDA in Australian population groups, those most vulnerable can be viewed in Figure 2.

ID may cause symptoms both in the presence and absence of anaemia or can be asymptomatic. Signs and symptoms depend significantly on the speed of anaemia onset, the disease severity, and the patient's characteristics.[16] General weakness, fatigue, poor concentration and pale skin are commonly associated with ID; however, given the critical role of iron in multiple biological processes, various signs and symptoms have been observed (see Table 2).

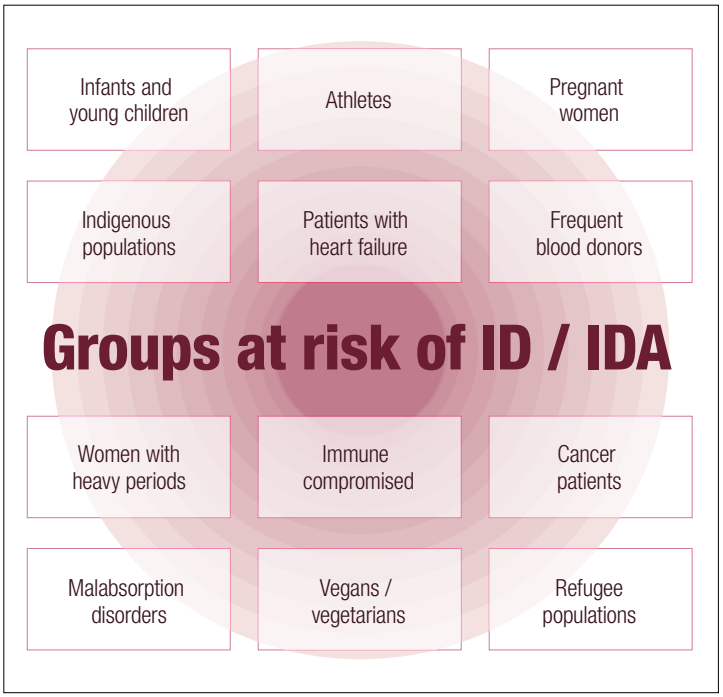
Diagnoses and evaluation

Adequate iron status indicates normal erythropoiesis and iron functions that are not limited by iron supply.[2] Although anaemia is defined as a

Table 1: Defining iron deficiency disorders[5,6]

Iron deficiency	Iron deficiency anaemia	Functional iron deficiency
Refers to low iron stores that do not meet the body's iron requirements. Ferritin is an indicator of iron stores and is the most sensitive marker for assessing iron deficiency.	Arises when there is insufficient iron to form normal red blood cells. The World Health Organisation (WHO) defines anaemia as a haemoglobin concentration below 130g/L in men, 120g/L in women and 110g/L in pregnant women and primary school children.	FID occurs when iron cannot be mobilised for erythropoiesis due to the action of elevated hepcidin that blocks the release of iron from storage. It is often associated with inflammatory states, autoimmune conditions, malignancy, and chronic renal failure.

Figure 2: Groups at risk of developing iron deficiency and iron deficiency anaemia



haemoglobin concentration below 130g/L for men, 120g/L in women and 110g/L for pregnant women and preschool children, ferritin is the most accurate test to diagnose IDA as it reflects iron stores.[19] However, given ferritin is an acute-phase reactant that increases during chronic inflammation, a diagnosis is not always straightforward.[16] In this case, it can be challenging to differentiate between IDA and anaemia of chronic disease, which can often co-exist.

Therefore, it is essential to consider the whole picture in determining iron status rather than relying on one single test. A thorough interpretation of various iron markers, including haemoglobin, serum iron, serum ferritin, transferrin, transferrin saturation and transferrin receptors, will direct the correct treatment approach. Moreover, these biomarkers are associated with advantages and disadvantages, and understanding their clinical significance is essential when evaluating iron status.

Table 2: Signs and symptoms of iron deficiency[17,18]

Signs	Symptoms
✓ Reduced resistance to infection ✓ Reduced thyroid function ✓ Cracks at the sides of the mouth ✓ Brittle nails ✓ Spooning of the nails ✓ Pale skin ✓ Pale nail bed or pale inside of the lower eyelid ✓ Brittle hair or hair loss ✓ Adverse pregnancy outcomes and increased perinatal maternal mortality ✓ Pica	✓ Fatigue ✓ Chest pain ✓ Shortness of breath ✓ Difficulty concentrating ✓ Irregular heartbeat ✓ Restless legs syndrome ✓ Weakness ✓ Dizziness ✓ Headache ✓ Sore tongue

Iron bioavailability

While oral iron supplementation is an effective first-line therapy in managing ID/IDA, its efficacy is often limited. The primary reason for the failure of iron therapy is often related to the frequent gastrointestinal side effects associated with commonly prescribed oral supplements, such as ferrous fumarate, ferrous sulphate and iron polymaltose. These problematic side effects may be a result of free radical generation through iron-induced redox cycling in the gastrointestinal lumen, promoting inflammation or changes to the microbiota.[20] Moreover, the oral bioavailability of such oral preparations is minimal, often requiring large therapeutic doses ranging from 150–300mg per day.[21]

Forms of iron with high bioavailability including iron bisglycinate may overcome these complications. This iron structure consists of one ferrous iron molecule attached to two glycine molecules by a covalent bond.[22] Once absorbed into the gastrointestinal mucosa via efficient amino acid uptake pathways, this chelated molecule is easily hydrolysed into individual components and released into the bloodstream.[23] It has also been suggested that this configuration protects the iron from dietary inhibitors, such as phytates, and prevents the precipitation of iron as insoluble ferric hydroxide in the pH of the small intestine.[24,25]

FERROCHEL™

FerroChel® is a patented, clinically trialled form of iron bisglycinate, which has demonstrated superior bioavailability and tolerability compared with other iron forms.

The greater bioavailability of iron bisglycinate to other iron preparations has been confirmed in multiple studies across various population groups, including infants,[26] children[27] and pregnant women.[28-30] In a study involving anaemic infants and young children, the bioavailability of iron bisglycinate (as FerroChel®) and ferrous sulphate was 90.9% and 26.7%, respectively.[26] In an additional trial involving male adolescents, iron bisglycinate was absorbed four times greater than ferrous sulphate when added to food, maintaining its efficacy on haematopoiesis.[31] Furthermore, in a randomised controlled trial including 200 children at risk of developing IDA, iron bisglycinate was more efficient at maintaining high ferritin concentrations six months after supplementation than ferrous sulphate.[32] Overall, these results suggest iron bisglycinate represents an attractive and promising alternative when managing iron deficiency disorders.

Synergistic nutrients

Vitamin C

It has been well established that vitamin C enhances the absorption of non-haem iron by reducing dietary ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), which is a requirement for the uptake of iron into the mucosal cells. Vitamin C promotes iron absorption by forming a soluble, stable chelate that stays in solution in the alkaline environment of the small intestine and allows entry into the intestinal wall.[13,37] The addition of 20mg of ascorbic acid has been shown to increase non-haem iron absorption by 39%.[18]

Table 3: Interpreting iron studies[33-36]

	Serum ferritin	Serum iron	Transferrin / Total iron binding capacity (TIBC)	Transferrin saturation (%)	Soluble transferrin receptor	Haemoglobin
Iron deficiency	↓	↓	↑	↓	↑	□ / ↓
Anaemia of chronic disease	□	↓	↓	↓	□	↓
Anaemia and inflammation	□	↓	□ / ↓	□ / ↓	↑	↓
Acute-phase response	↑	↓	↓	↓	□	↓
Haemochromatosis	↑	↑	↓	↑	↓	□
Secondary iron overload	↑	↑	□ / ↓	↑	↓	□

KEY: ↑ = increased; ↓ = decreased; □ = normal

Lactoferrin

Lactoferrin is an iron-binding protein abundantly expressed in human breast milk and the milk of other mammals. It is also present in other body fluids such as tears, saliva, bile, pancreatic juice and genital and nasal secretions. Produced by circulating neutrophils during infection and inflammation, lactoferrin is functionally and structurally similar to transferrin.[38] Research indicates lactoferrin has a high affinity for sequestering iron and is an essential regulator of iron homeostasis. Since lactoferrin binds iron with high affinity in the small and large intestine, it may also act as a bacteriostatic agent for withholding iron from pathogens, whose growth and virulence depend on an adequate iron supply.[39] Within exocrine secretions, lactoferrin, by virtue of its iron-binding ability, ensures that free iron concentration in human secretions does not exceed levels that may create iron precipitation, reactive oxygen species (ROS) and microbial growth.[40]

Australian PURE nFERRIN

PUREnFERRIN™ is an Australian sourced, lactose free and ultra-pure lactoferrin. The specialised manufacturing process preserves protein structure and lactoferrin functionality.

Lactoferrin and iron homeostasis

Increasing intestinal iron absorption

Lactoferrin plays a significant role in iron uptake by the intestinal mucosa. Almost all iron in human breast milk is bound to lactoferrin, which suggests a strong involvement in iron absorption in the underdeveloped GIT of newborns. Lactoferrin can directly supply iron to intestinal epithelial cells through a unique lactoferrin-binding receptor.[41] Expression of this receptor is found abundantly along the infant small intestine; however, high amounts have also been observed in the duodenum, jejunum and ileum, allowing for uptake along the entire small intestine. Conversely, non-haem iron absorption occurs exclusively in the duodenum; this may explain why iron absorption is lower in infants on formulas containing ferrous iron.[42]

Modulating protein and inflammatory cytokines

Lactoferrin appears to supply iron to the intestinal epithelial cells and modulates proteins involved in maintaining iron status. It is well established that systemic iron homeostasis is influenced by inflammation and infection. Lactoferrin has shown anti-inflammatory and bacteriostatic action, which may also enhance iron uptake and distribution.[41] Inflammatory cytokines such as IL-6 induce the production of hepcidin, a circulating peptide hormone produced by hepatocytes. As previously discussed, dysregulation of hepcidin by inflammation has been recognised as a mechanism of action for the development of iron disorders.[40] Lactoferrin has been shown to significantly reduce IL-6 concentrations in pregnant women suffering from ID/IDA, thus restoring iron homeostasis. In contrast, ferrous sulphate supplementation increased these cytokines and consequently failed to increase plasma iron.[43]

Sequestering iron during infection

Lactoferrin is produced endogenously by neutrophils during infection as a measure to reduce available iron. This has an inhibitory effect on pathogen duplicity and metabolic processes.[44] Chronic infection in the gastrointestinal tract (GIT) by pathogens including *Helicobacter pylori* and parasites can significantly contribute to ID by reducing available iron for absorption.[46] Lactoferrin may sequester iron in the GIT and carry it across the intestinal mucosa, making it available for the body's own iron pool.[47] The unique properties of lactoferrin make it an appealing supplement for treating and preventing ID and IDA.

Correcting iron status in various population groups

Pregnancy

IDA during pregnancy continues to be one of the most important public health problems, affecting 32 million women worldwide.[48] Iron requirements increase roughly by 10-fold during pregnancy due to increased blood volume and supply to the foetus. Maternal serum ferritin markedly decreases between weeks 12 and 25, potentially due to iron utilisation for the expansion of maternal red blood cell mass.[49] IDA affects the mother's general well-being and increases the risk of preterm birth, foetal growth retardation, low birth weight, and perinatal death.[50] Moreover, infants born to iron deficient mothers are at increased risk of developing IDA, which may go undetected at birth.[51]

Iron

While ferrous sulphate is the most common treatment recommended for ID and IDA in pregnancy, its ability to exert any significant effects is limited.[40] Large quantities of ferrous sulphate are often required, which is associated with numerous side effects, often affecting patients' adherence to treatment.[28] Alternatively, iron bisglycinate has been shown to exert superior efficacy in increasing haematological markers compared to ferrous sulphate in pregnant women with IDA.[28] In a randomised, double-blind clinical trial, 187 pregnant women at 14–18 weeks gestation with mild to moderate IDA, received iron bisglycinate (27mg iron/day) or ferrous sulphate (FS) (100mg iron/day) for 8 weeks. The mean increase in haemoglobin and ferritin levels in the iron bisglycinate group was significantly higher ($P < 0.0001$) than in the ferrous sulphate group, even at the lower dose. Moreover, the rate

Figure 3: Serum ferritin levels in pregnant women with iron deficiency anaemia before and after iron treatment for 8 weeks[28]

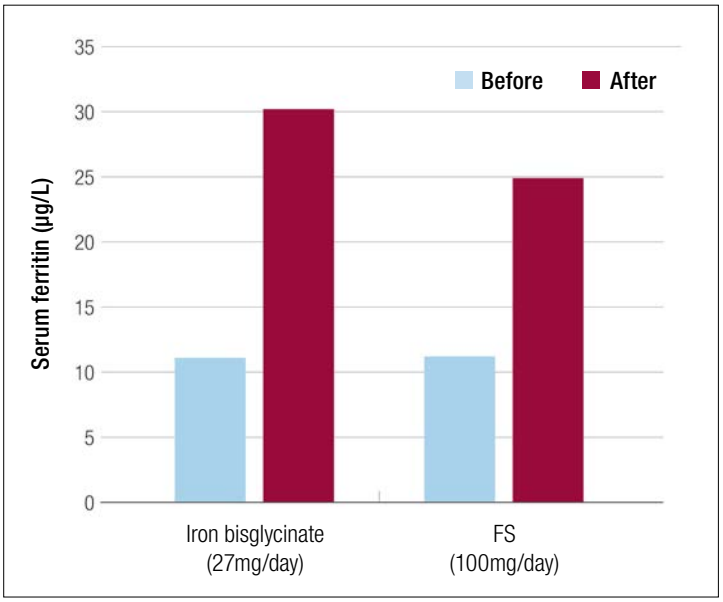
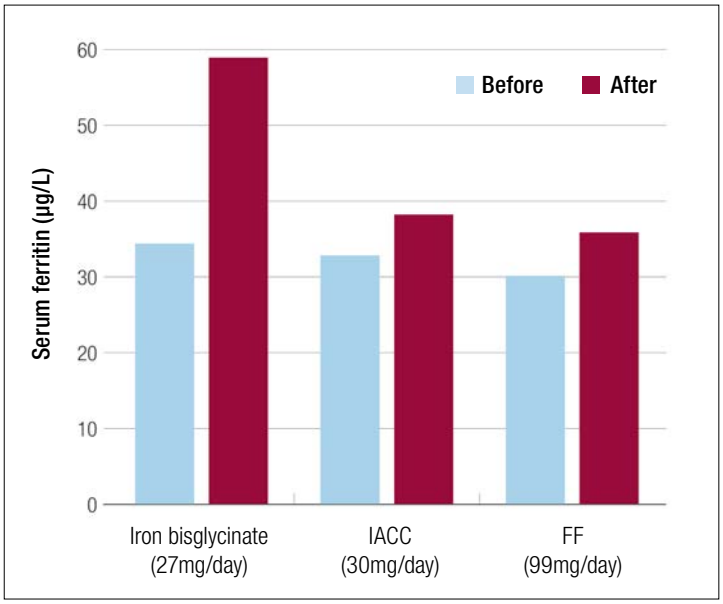


Figure 4: Serum ferritin levels in pregnant women with iron deficiency anaemia before and after iron treatment for 1 month[29]



CLINICAL RESEARCH – Lactoferrin in pregnancy

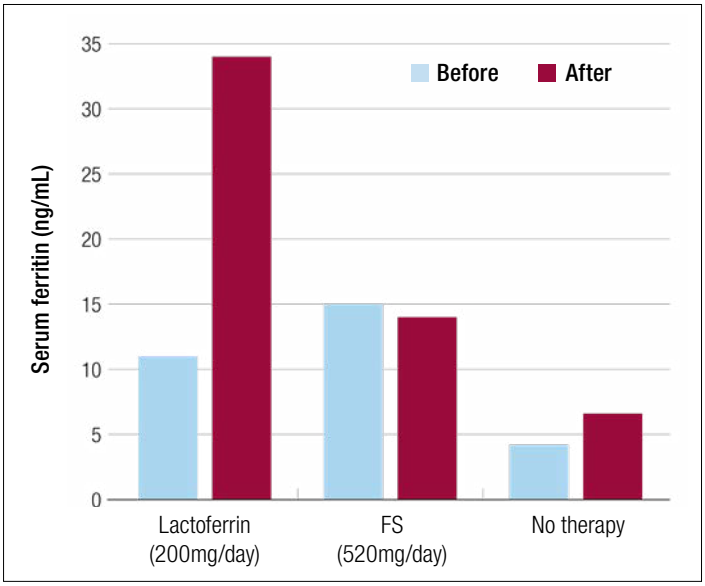
Study 1: Lactoferrin efficacy versus ferrous sulphate in treating iron disorders in pregnancy

In a single centre, phase IV open, prospective and randomised clinical trial, 71 women suffering from IDA in their third trimester of pregnancy were randomised to receive either lactoferrin (100mg, twice a day) or ferrous sulphate (520mg per day) for 30 days.[43] Twelve women refused therapy and were consequently allocated to the study control group.

Haematological parameters, including red blood cells, haemoglobin, total serum iron, serum ferritin and haematocrit, significantly improved in women treated with lactoferrin ($P < 0.0001$). Conversely, these parameters did not increase significantly in women receiving ferrous sulphate or those refusing therapy (see Figure 5).

Furthermore, IL-6 levels significantly decreased in the lactoferrin treatment group ($P < 0.0001$), while a significant rise was observed in women receiving ferrous sulphate ($P = 0.0015$) (see Figure 6). Interestingly, the failure of ferrous sulphate to enhance plasma iron may be related to increased IL-6 levels. This inflammatory cytokine is associated with the down-regulation of ferroportin expression, thus hindering iron export from tissues.[43]

Figure 5: Serum ferritin levels in pregnant women at third trimester suffering ID or IDA treated with lactoferrin, ferrous sulphate or no therapy[43]



of adverse reactions was significantly higher in the ferrous sulphate group (P = 0.001) (see Figure 3).

These results align with previous clinical trials assessing the efficacy of iron bisglycinate (as FerroChel®) compared to other iron preparations. In one study, 15mg of iron bisglycinate was more effective than 40mg of ferrous sulphate in preventing iron depletion in pregnancy.[30] Moreover, iron bisglycinate increased serum ferritin levels more significantly than iron amino acid chelate (IAAC) and ferrous fumurate (FF) in a comparative study of pregnant women with IDA (P < 0.05) (see Figure 4).[29]

Lactoferrin

Concurrently, pregnancy is strongly associated with an increase in oxidative stress. As previously mentioned, pro-inflammatory cytokines, specifically IL-6, promote hepcidin synthesis. Enhanced hepcidin activity leads to reduced plasma iron levels and anaemia induction.[40] Significantly increased levels of pro-inflammatory cytokines have been measured in women experiencing unexplained recurrent spontaneous abortions compared to normal pregnant women at similar stages.[52]

Figure 6: Serum IL-6 levels in iron deficient pregnant women treated with lactoferrin, ferrous sulphate or no therapy for 30 days[43]

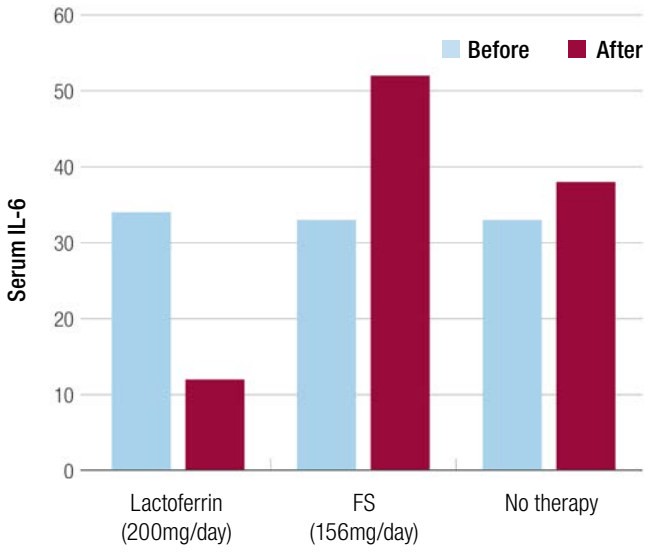


Table 4: Assessment of iron studies[33-36,45]

Iron studies	Function	Clinical significance	Reference ranges
Haemoglobin	Main component of red blood cells and carries oxygen to cells.	Low haemoglobin may be the result of iron deficiency, blood loss or chronic illness. Above normal levels may indicate dehydration, excessive production of red blood cells or lung disease.	**Men:** 130–180 g/L **Women:** 115–165 g/L
Serum ferritin	Ferritin is the intracellular storage form of iron. Ferritin levels are believed to reflect global iron stores in bodily tissues.	Sensitive indicator of iron deficiency. However, as ferritin is an acute-phase protein, it is raised in inflammation, liver disease and malignancy. Checking C-reactive protein (CRP) and other inflammatory markers may provide a clearer picture.	**Adult female:** 15–200µg/L* *At least 50µg/L to prevent fatigue and assist energy production **Pregnant female:** <30 (low) <15 (depleted) **Adult male:** 30–300µg/L **Child:** 20–200µg/L
Serum iron	Circulating iron that is bound to transferrin.	Highly variable and provides little significance when viewed in isolation. Levels affected by dietary iron intake, contraceptive pill, inflammation and infection.	10–30µmol/L
Transferrin / TIBC	TIBC measures the maximum amount of iron bound to transferrin. TIBC is a direct measurement of transferrin.	Values may increase in iron deficiency, contraceptive use and pregnancy, and may decrease in iron overload or inflammation.	45–80µmol/L
Transferrin saturation (%)	The percent of transferrin iron-binding sites that are occupied by iron. This is a marker of circulating iron.	Levels may rise in iron overload and fall in iron deficiency; however, it does not quantitatively reflect iron stores. A rise in serum iron due to dietary intake may cause increased saturation levels.	<15% in association with an elevated TIBC is indicative of iron deficiency anaemia. >45% is suggestive of iron overload.
Soluble transferrin receptor (sTfR)	sTfR for transferrin is membrane-bound and are present on cell surfaces.	Receptors increase in iron deficiency, megaloblastic anaemia and thalassaemia.	1.8–4.6mg/L

It has also been demonstrated that significantly higher levels of IL-6 are present in the plasma of patients with preeclampsia compared to healthy pregnant women.[53] Lactoferrin offers a safe and effective alternative for treating and preventing ID and IDA in pregnancy due to its ability to sequester and deliver iron to epithelial cells and modulate important proteins involved in systemic iron homeostasis.

Multiple clinical trials have demonstrated lactoferrin to have either the same or greater efficacy than ferrous sulphate in improving haemoglobin, total serum iron and serum ferritin values amongst iron-deficient pregnant women.[7,54-58] A systematic review and meta-analysis involving 600 pregnant women also found lactoferrin to be as effective as ferrous sulphate in improving haematological parameters.[59] The authors concluded that lactoferrin should be the iron agent of choice for treating IDA in pregnancy due to the significantly fewer gastrointestinal side effects associated with lactoferrin supplementation.

Concerning safety, 16.5% of women in the ferrous sulphate group withdrew from the trial due to adverse effects, while women taking lactoferrin did not experience any discomforts. Finally, five miscarriages were reported among the ferrous sulphate treated women, potentially due to low iron status and high levels of IL-6.[54]

CLINICAL RESEARCH – Lactoferrin in pregnancy

Study 2: Anaemia + anaemia of inflammation in pregnant and non-pregnant women

An interventional study compared the efficacy of lactoferrin (200mg) to ferrous sulphate (105mg elemental iron) in treating anaemia of inflammation in 198 pregnant and non-pregnant women with minor β-thalassemia or hereditary thrombophilia (HT).[7]

After 30 days, lactoferrin was more efficient than ferrous sulphate in treating anaemia of inflammation in HT women by decreasing serum IL-6 and hepcidin, resulting in increased haemoglobin, serum iron and serum ferritin. In women with minor β-thalassemia, lactoferrin decreased IL-6 and increased total serum iron, while these levels remained unchanged in the ferrous sulphate group.

While further studies are warranted, these results show lactoferrin has greater efficacy than ferrous sulphate in the treatment of anaemia and anaemia of inflammation through its ability to down-regulate IL-6 and hepcidin.[7]

Study 3: ID/IDA in hereditary thrombophilia pregnant women

Another interventional study evaluated the safety and efficacy of lactoferrin (200mg) compared to ferrous sulphate (520mg) in treating ID/IDA in 253 pregnant women with HT.[54] At delivery, haematological parameters were significantly higher in the lactoferrin group than the ferrous sulphate arm ($P < 0.0001$). Moreover, serum IL-6 levels significantly decreased in lactoferrin treated women, whereas an increase in these levels was detected in the ferrous sulphate group. The ability of lactoferrin to restore iron homeostasis and attenuate inflammation could represent a vital and safe therapy against ID/IDA in HT pregnant women.

Infants and children

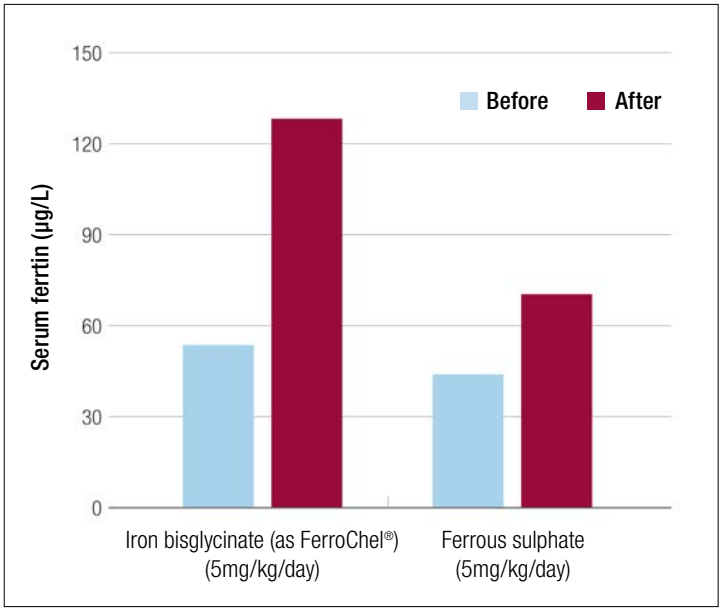
The consequences of ID or IDA in early childhood are often severe and may result in neurodevelopmental and motor delays, which can be viewed several years after the deficiency is corrected.[27,60] In children, iron loss occurs in bile, urine, faeces and by the introduction of cow's milk during the first year of life (primarily due to its low iron content).[61] Primary prevention of ID or IDA can be achieved through the fortification of foods and dietary education.[62] However, due to the greater physiological requirements within the first two years of life, preventative iron supplementation may be required.[61]

Iron

Various clinical trials have reported greater efficacy and safety of iron bisglycinate (as FerroChel®) than other iron preparations in treating ID and IDA in infants and children. In a study of infants aged six–36 months with IDA, iron bisglycinate was absorbed 3.4 times greater than ferrous sulphate.[26] Moreover, a significant increase in plasma ferritin was observed in children receiving iron bisglycinate (5mg/kg of body weight) compared to ferrous sulphate ($P < 0.005$) (see Figure 7).

An observational, prospective multi-centre study monitored the effects of various iron preparations, including ferrous sulphate (2mg/kg or 4mg/kg), ferric iron salts (2mg/kg), iron bisglycinate (0.45mg/kg) and liposomal iron (0.7–1.4mg/kg) in 107 children aged three months to 12 years with IDA.[63] While ferrous sulphate showed the greatest tendency to increase haemoglobin levels, iron bisglycinate had comparable efficacy, even at a much lower dose.[63] Supplementation with iron bisglycinate at 0.75mg/kg/day also demonstrated comparable efficacy to iron sulphate at 3mg/kg/day in 300 preterm infants.[64] Lastly, in a double-blind study, children with IDA aged one to 13 years were randomly assigned to receive iron bisglycinate (as FerroChel®) or polymaltose iron for 45 days.[27] While both treatments lead to increased haemoglobin, mean corpuscular volume, red cell distribution width and decreased transferrin levels, only the iron bisglycinate (as FerroChel®) group demonstrated a significant increase in ferritin levels

Figure 7: Serum ferritin levels in infants with IDA before and after administration of 5mg/kg/d of iron bisglycinate (as FerroChel®) or ferrous sulphate for 28 days[26]



and mean corpuscular haemoglobin. Furthermore, iron bisglycinate (as FerroChel®) increased ferritin levels in individuals with low initial haemoglobin levels, suggesting that the absorption is regulated by the iron demand. This factor implies that iron bisglycinate is a safe compound for long-term supplementation, even after the normalisation of haemoglobin levels (see Figure 8).[27]

Lactoferrin

Lactoferrin has been shown to significantly increase haemoglobin ($P = 0.001$), serum ferritin ($P = 0.001$) and total iron ($P = 0.038$) after 30 days of treatment in 94 school children with IDA.[65] Moreover, in a recent randomised crossover trial involving 25 infants, the addition of 1.4g of lactoferrin to maize porridge containing 1.5mg of iron, increased iron absorption by 56% compared to meals without lactoferrin.[66] Lactoferrin may therefore offer a safe way to improve the efficacy of iron fortificants aimed at young children with ID.

Children with cerebral palsy (CP) are particularly susceptible to malnutrition and dietary deficiencies due to chewing and swallowing difficulties, self-feeding issues and inadequate diets. An ID may negatively impact functional abilities and muscle strength in children with CP, indicating a need for early identification to prevent neurodevelopmental consequences.[67] A recent study compared the efficacy of lactoferrin with iron polymaltose in the treatment of IDA in children aged one to 10 years with CP.[68] Haemoglobin and serum ferritin levels were significantly higher in those receiving lactoferrin compared to iron polymaltose ($P = 0.001$ and $P = 0.033$ respectively), and constipation was less likely to occur ($P = 0.049$). The authors concluded lactoferrin was superior to iron polymaltose as an oral iron replacement therapy in children with CP and IDA.

Attention-deficit hyperactivity disorder

Iron

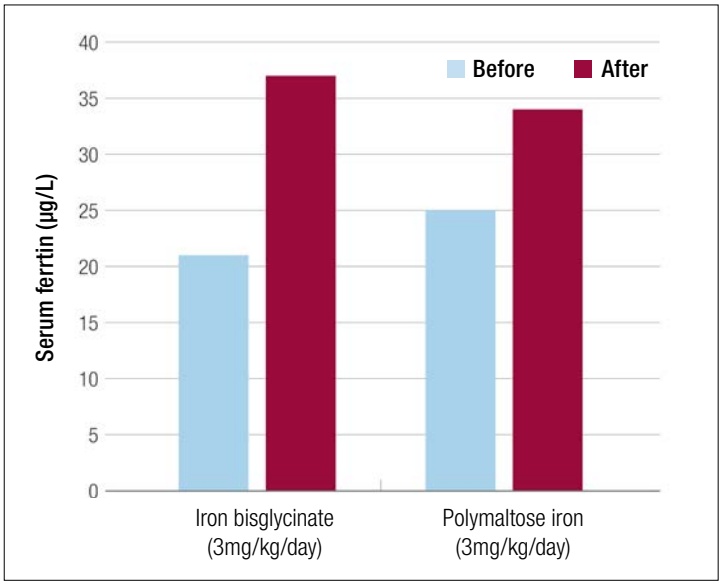
IDA is estimated to affect approximately 20% of infants, and a greater percentage are assumed to have milder iron deficiencies, leaving them at risk of brain development impairment.[69] Children with attention-deficit hyperactivity disorder (ADHD) are more commonly affected by ID;[70,71] in particular, ID may contribute to behavioural problems due to iron's influence on the metabolism of dopamine and other catecholamine's.[72] One study observed a significant improvement in ADHD symptoms after non-anaemic participants were supplemented with 5mg/kg of body weight of iron for 30 days.[73] A later study similarly found oral iron supplementation (80mg/day) for 12 weeks improved ADHD symptoms in children with low ferritin levels.[74] Ferrous sulphate was used in these studies, however, iron bisglycinate has showed greater efficacy and safety in various studies involving children[64,26] and should be considered when treating ID in ADHD patients.

Coeliac disease

Iron

As iron absorption primarily occurs in the duodenum and the jejunum, individuals with malabsorption disorders such as coeliac disease (CD) are often at risk of developing IDA.[75] While ferrous sulphate remains the gold standard for treating iron-depleted patients, regardless of the underlying disease,[76] a recent study has demonstrated the efficiency and safety of iron bisglycinate in the treatment of IDA in children aged three to 18 years with active CD following a gluten-free diet.[77] While further studies are required to solidify these results, iron bisglycinate poses an effective alternative for patients with malabsorption disorders, particularly where other iron forms have failed.

Figure 8: Serum ferritin levels in iron deficient children treated with iron bisglycinate (as FerroChel®) or polymaltose iron at 3mg/kg/day for 45 days[27]



Cancer

Iron

Anaemia is independently associated with shorter survival, decreased quality of life (QoL), and appears to occur more frequently in patients with tumour recurrence, advanced stages of the disease, and those receiving anticancer treatment.[78-80] The pathogenesis of anaemia in cancer is often multifactorial, including malnutrition, malabsorption, haemolysis, acute or chronic bleeding, myelosuppressive chemotherapy or radiotherapy, bone marrow infiltration or chronic illness.[81] Given the significant impact of anaemia on QoL, disease progression and survival, correcting anaemia is of paramount importance in cancer patients.

While iron stores can be replenished through oral or parenteral administration, studies have shown oral ferrous sulphate to be inferior to intravenous iron at improving haemoglobin levels in cancer patients.[82] The use of ferrous sulphate is primarily limited by its reduced bioavailability and gastrointestinal side effects, which may add to the discomfort associated with antineoplastic treatments.[78] A study involving 24 patients with various solid tumours (breast, colorectal and gastric) and mild IDA, assessed the efficacy and toxicity of oral iron bisglycinate compared to ferrous sulphate at improving haematology markers.[78] Patients were randomised to receive 28mg of iron bisglycinate for 20 days, followed by 14mg for 40 days, or oral ferrous sulphate at 105mg per day for 60 days. At the lower doses, iron bisglycinate improved haemoglobin and ferritin levels similar to the conventional dose of 105mg ferrous sulphate, with lower gastrointestinal toxicities.[78] These results suggest iron bisglycinate is a safe therapeutic option for cancer patients with mild IDA.

Lactoferrin

Functional iron deficiency (FID) refers to an inability to effectively utilise iron rather than a deficiency caused by inadequate intake. This

form of deficiency often arises in cancer patients in the absence of bleeding, haemolysis, cancer infiltration of bone marrow, renal or liver failure.[83] It is considered to be caused by the release of pro-inflammatory cytokines from the immune system and the tumour itself, resulting in chronic inflammation and oxidative stress.[83] Cytokines induce changes in iron balance, erythropoietin production, survival of circulating erythrocytes and alterations in energy metabolism – all of which induce anaemia.[83]

Lactoferrin may improve iron metabolism and correct FID by modulating inflammatory cytokines and oxidative stress. In an open-label study, anaemic cancer patients were randomised to receive 200mg of oral lactoferrin or 125mg of intravenous iron, both in combination with recombinant human erythropoietin. Both arms showed a significant increase in haemoglobin and similar iron levels throughout the treatment. However, the lactoferrin arm showed a significant decrease in elevated ferritin stores and an immediate reduction in inflammatory markers, erythrocyte sedimentation rate and CRP. These results indicate lactoferrin's capacity to normalise serum iron by improving iron mobilisation in acute or chronic inflammation.[83]

Athletes

Lactoferrin

Sports anaemia is a common condition experienced by endurance athletes, often caused by insufficient nutrient intake, increased haemolysis related to physical activity, increased red cell membrane fragility due to inadequate oxygen, and loss of iron in sweat, urine and stools. Sports anaemia directly affects exercise performance due to a lack of oxygen supply to tissues. Insufficient iron stores are also responsible for slowing the removal of lactic acid during exercise, resulting in earlier onset fatigue.[84]

A study involving female long-distance runners found lactoferrin (1.8g per day) in combination with iron (6mg per day) prevented a significant drop in ferritin, serum iron, and red blood cell count compared to taking iron alone. Moreover, red blood cell count was significantly higher in the lactoferrin and iron group compared to iron alone. In addition, after a 3km run, lactic acid levels were significantly higher in the control group than the lactoferrin group when measured at the end of the eight week trial.[84] The results of this study suggest supplementing with lactoferrin alongside iron is beneficial in preventing IDA, particularly among female long-distance runners who are at greater risk of developing this condition.[84]

Dosage safety and clinical tips

Iron dosing

Adults

In Australia, the recommended dose to treat IDA is 100–200mg of elemental iron daily.[5] Lower doses containing 30–60mg of elemental iron may be preferential in patients with mild ID or those who experience gastrointestinal upset. Oral iron therapy should be continued for three months after anaemia has been corrected in order to replenish stores.[19]

Table 5: Dose suggestion of iron bisglycinate for correcting IDA and iron homeostasis in adults, according to serum ferritin levels

Serum ferritin	Dose sugggestion (iron bisglycinate)
<15µg/L	75–100mg elemental iron
15-30µg/L	50–75mg elemental iron
30-50µg/L	25–50mg elemental iron
>50µg/L	0–25mg elemental iron (depending on underlying factors such as menstruation, malabsorption syndromes, pregnancy)

Infants and children

In clinical trials, children aged one to 13 years diagnosed with IDA were supplemented with 3mg/kg of body weight of iron bisglycinate (as FerroChel®) per day.[27] It is recommended to continue oral iron therapy for two to three months after haemoglobin has normalised to replenish iron stores.[85]

Evidence on intermittent iron dosing

Controversy exists surrounding the most efficient way of administering iron supplements. While intermittent dosing has gained some interest, the currently available evidence suggests that daily use is still superior to intermittent dosing for correcting a deficiency.

Various Cochrane reviews have assessed the benefits of intermittent iron dosing compared to daily supplementation across multiple population groups. Findings of one review found intermittent iron dosing in pregnancy produces similar maternal and infant outcomes as daily supplementation; however, those receiving daily iron were less likely to present with anaemia near term.[8] In an additional Cochrane review, compared to daily supplementation, intermittent iron dosing in menstruating adolescents and adults produced similar effects on improving haemoglobin concentrations but was less effective for raising ferritin levels.[86] Lastly, intermittent iron supplementation was efficacious at improving haemoglobin concentrations in children younger than 12 years of age when compared with a placebo or no intervention but was less effective than daily supplementation to prevent or control anaemia.[87]

Moreover, while only demonstrated with ferrous sulphate and in women with low iron, it has been inferred that oral doses of supplemental iron acutely increase serum hepcidin, reducing iron absorption from subsequent doses.[88] Given lactoferrin decreases IL-6 concentrations, which modulates hepcidin expression, and has been shown to reduce hepcidin expression in clinical studies,[7] the addition of lactoferrin to iron supplementation may overcome this potential issue.

Lactoferrin dosing

In clinical trials, the dosage of lactoferrin to treat ID or IDA was 100mg, twice a day (200mg). However, doses of up to 3.6g have been used in human studies without side effects,[89,90] suggesting higher doses are considered safe.

Timing

Iron competes with various foods, herbs, and minerals for absorption, such as tannins, phytates, oxalates, calcium, zinc and manganese,[18,91] and it is therefore suggested that administration away from food is preferable. However, iron bisglycinate has been found to be well-tolerated and effective when given with food in clinical studies. In addition, lactoferrin and vitamin C may enhance the absorption of iron from foods. While these ingredients can be given with or without food, administration with food is likely to facilitate optimal tolerability, compliance and iron repletion.

Considerations and drug interactions

Dosing may need to be adjusted in various conditions that limit iron absorption, such as malabsorption syndromes, disorders of insufficient digestive secretions, and *H.pylori* infection.[18] Iron supplementation should be avoided in patients with haemochromatosis or iron loading anaemias, such as thalassaemia and sideroblastic anaemia.[18]

The concurrent use of iron with certain drugs has been shown to reduce the efficacy of either the medication or iron absorption. Summarised below are some of the known interactions and the prescribing recommendations to maximise clinical effectiveness and safety.

Table 6: Potential iron interactions[18,92]

Drug	Mechanism of action	Prescribing recommendation
Antacids, proton pump inhibitors, H2 receptor antagonists	Substances that alter gastric pH may reduce the absorption of iron.	Prescribe iron supplementation at least two hours away from antacids to improve efficacy.
Antibiotics	**Tetracyclines –** iron supplementation is known to interact with tetracyclines through the formation of insoluble complexes, resulting in decreased absorption of both drug and iron supplement.	Take iron supplements at least three hours away from tetracyclines.
	Quinolones – iron is known to interact with quinolones through the formation of insoluble quinolone-iron complexes, significantly decreasing drug absorption.	Ensure iron supplementation is taken at least two hours away to prevent decreased drug absorption.
Antihypertensive agents	**Methyldopa –** iron supplements are known to reduce drug absorption and consequently the drug effect.	If iron supplementation is essential, separate the dose by two hours. Regular blood pressure monitoring is essential.
	Captopril – iron supplementation reduces unconjugated captopril blood concentrations due to the formation of iron-captopril complexes in the GIT.	Separate the dose of captopril and iron by at least three hours is likely to reduce the extent of this interaction.
Bisphosphonates	Bisphosphonates are known to form complexes with multivalent cations, such as iron. While not specifically studied in humans, this may lead to reduced absorption and effectiveness.	Prescribe iron supplementation at least two hours away from bisphosphonates.
Dolutegravir	Iron can reduce how much dolutegravir the body absorbs.	To avoid this interaction, prescribe dolutegravir at least two hours before or six hours after iron supplementation.
Levodopa, Carbidopa	Co-administration of iron decreases both levodopa and carbidopa via the formation of stable complexes.	Dose separation of pharmaceuticals and iron supplements by at least three hours is recommended.

Drug	Mechanism of action	Prescribing recommendation
Levothyroxine	Iron supplementation may decrease the absorption of thyroid medication.	To reduce severity of the interaction, separate doses by two to four hours. Regular monitoring of thyroid function may be indicated.
Penicillamine	High iron doses reduces penicillamine absorption, potentially due to chelation of iron to penicillamine in the intestines.	Take iron supplements three hours or more after penicillamine to prevent interactions.

Summary of clinical studies comparing iron forms

A summary of the clinical trials comparing the different iron forms can be viewed below. In all included studies, iron bislgycinate was found to be more efficient than other iron formulations in preventing or treating ID/IDA in pregnant women, infants, children and cancer patients.

Table 7: Summary of clinical trials

Condition	Objective	Dosage and duration	Outcome
IDA in pregnancy[28]	To compare the efficacy and tolerability of iron bisglycinate versus ferrous sulphate.	**n** = 187 **Iron bisglycinate:** 27mg daily **Ferrous sulphate:** 567.6mg daily **Duration:** 8 weeks	The mean increase in haemoglobin levels after treatment in the iron bisglycinate group was statistically significant compared to the ferrous sulphate group ($P < 0.0001$). The rate of side effects was significantly higher in the ferrous sulphate group ($P = 0.001$). Pregnant women with IDA could be supplied with iron bisglycinate, which is more efficient in increasing haemoglobin levels than ferrous sulphate.
IDA in pregnancy[30]	To compare the effectiveness of iron bisglycinate and ferrous sulphate in controlling iron deficiency in pregnant women.	**n =** 145 **Iron bisglycinate (as FerroChel®):** 15mg per day **Ferrous sulphate:** 40mg per day **Duration:** <20 weeks gestation until 40 weeks	It was concluded at the end of the study that daily supplementation with iron bisglycinate (as Ferrochel®) was significantly more effective than ferrous sulphate in preventing iron depletion, despite the lower dose.
IDA in pregnancy[92]	To compare iron bisglycinate efficacy and tolerability versus ferrous sulphate in preventing ID and IDA in pregnant women.	**n =** 80 **Iron bisglycinate:** 25mg daily **Ferrous sulphate:** 50mg daily **Duration:** From 15-19 weeks of gestation to delivery	In preventing ID and IDA in pregnant women, low dose iron bisglycinate appears to be as effective as ferrous sulphate. The frequency of gastrointestinal complaints was lower in the bisglycinate group ($P = 0.001$), and newborns weight was slightly higher in the bisglycinate group compared to sulphate group ($P = 0.09$).
IDA in pregnancy[29]	To compare the efficacy and tolerability of iron bisglycinate, iron amino acid chelate, and ferrous fumarate in treating anaemic pregnant women.	**n** = 300 **Iron bisglycinate (as FerroChel®):** 27mg daily **Iron amino acid chelate:** 30mg, twice daily **Ferrous fumarate:** 198mg, three times daily **Duration:** 1 month	A significant increase in haemoglobin was seen in all three groups ($P < 0.05$). Increase in ferritin with iron bisglycinate was significantly more than other treatments ($P < 0.05$). Nausea, vomiting, epigastric pain did not significantly co-exist with iron bisglycinate. Therefore, it can be concluded that iron bisglycinate can be considered the best effective medication with tolerable side effects for treatment and prevention of IDA in pregnancy.

Condition	Objective	Dosage and duration	Outcome
Anaemic children[27]	To compare the efficacy of iron bisglycinate and iron polymaltose in anaemic children.	**n** = 20 **Iron bisglycinate:** 3mg/kg/day **Iron polymaltose**: 3mg/kg/day **Duration:** 45 days	Both treatments resulted in significant increases in haemoglobin levels, mean corpuscular volume and cell distribution width, and reduced transferrin levels. However, only the iron bisglycinate treatment significantly increased ferritin and mean corpuscular haemoglobin levels. These results provide preliminary evidence to suggest a greater efficacy of iron bislgycinate than iron polymaltose in improving iron stores.
IDA in infants and young children[26]	To evaluate the efficacy of iron bisglycinate to ferrous sulphate in infants (aged six – 36 months) with IDA.	**n** = 300 **Iron bisglycinate:** 5mg/kg/day **Ferrous sulphate:** 5mg/kg/day **Duration:** 28 days	Both groups had significant haemoglobin increases ($P < 0.001$), but only the group treated with iron bisglycinate had significant increases in plasma ferritin ($P < 0.005$). Apparent iron bioavailabilities were calculated at 26.7% for ferrous sulphate and 90.9% for iron bisglycinate. Iron bisglycinate is the iron of choice for treating infants with IDA because of its high bioavailability.
IDA in preterm infants[64]	To evaluate the efficacy of iron bisglycinate to ferrous sulphate in preterm infants.	**n** = 300 **Iron bisglycinate:** 0.75mg/kg/day **Ferrous sulphate:** 3mg/kg/day **Duration:** Birth to discharge	The higher bioavailability of iron bisglycinate, at a quarter of the dose, achieved equivalent efficacy to iron sulphate. Iron bisglycinate may be an alternative to iron sulphate in the prevention and treatment of preterm newborn anaemia.
Mild IDA in cancer patients[78]	To compare the efficacy and toxicity of iron bisglycinate and ferrous sulphate in cancer patients with mild IDA.	**n** = 24 **Iron bisglycinate:** 28mg/day for 20 days, then 14mg/day for 40 days **Ferrous sulphate:** 105mg/day for 60 days **Duration:** 60 days	The study found iron bisglycinate given at 30mg daily for 20 days and then 15mg daily for 40 days to have similar efficacy and likely lower gastrointestinal toxicity than ferrous sulphate given at the conventional dose for the same time.

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