IRON DEFICIENCY ANAEMIA- A MINI REVIEW
PRATHIBHA G¹*, SUBASH VIJAYAKUMR¹, G. VIJAY KUMAR²

ABSTRACT
This article describes the iron deficiency anaemia (IDA) and its clinical manifestation, aetiology, diagnosis, prevention and management, given in a concise overview of the concept and the way of biomedical literature retrieval from worldwide biomedical databases described in the scientific and professional medical journals that are currently available using the key phrases, Causes and Management. Our article suggest that IDA is a major clinical condition in developing country especially India, should be prevented by providing good dietary supplements for poor children and adults population. In future, create awareness among public, and encourage the mothers for breast feeding and there is a need for effective newer diagnostic technique.

KEYWORDS
Iron deficiency anaemia, Reticulocytic haemoglobin, Ferrous sulphate, and Seafood.

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INTRODUCTION

Iron deficiency (ID) is a state in which there is insufficient iron to maintain the normal physiological function of blood and tissues, such as the brain and muscles. In human nutrition, iron is of great importance as it is a necessary mineral for body function and good health. In the body, iron is necessary for the formation of haemoglobin the pigment that carries oxygen to the tissues from the lungs. 70 to 95 percent iron of human bodies is present in haemoglobin in circulating red blood cells. The more severe stages of ID are associated with anaemia. Iron-deficiency anaemia (IDA) occurs when the haemoglobin concentration is below two standard deviations of the distribution mean for haemoglobin in an otherwise normal population of the same sex and age.1 IDA is generally characterized by a haemoglobin level of less than 110 g/L, plus a measure of poor iron status.2

EPIDEMIOLOGY

Iron deficiency anaemia is a serious and widespread public health concern in both developing and developed countries. It affects 20-50% of the world’s population and is common in young children.3 The prevalence of Iron deficiency anaemia (IDA) is high in developing countries than in the developed countries due to poverty, inadequate diet, high incidence of communicable diseases, pregnancy/lactation and low immunity. A review by Kanani S et al., reported that, anaemia in adolescent girls revealed that > 70% of adolescent girls in low income communities had haemoglobin levels <110 g/L. When WHO cut off of 120 g/L was applied, the prevalence was even higher (80-90%) 4. Around the world, IDA affects approximately 750 million children.5 Using anaemia as an indicator, it has been found that at least 30% to 40% of children and pregnant women in industrialized countries are iron deficient.6,7 Data from the third National Health and Nutrition Examination Survey (NHANES III) in developed countries indicated that 3% of children aged 12–36 months and less than 1% in the 37–60 months age group had IDA.8

IRON CYCLE9

Iron facts

- All body cells need iron. It is crucial for oxygen transport, energy production, and cellular growth and proliferation.
- The human body contains an average of 3.5 g of iron (males 4 g, females 3 g).
- The typical daily American diet contains 10–20 mg of iron.
- Only about 10% of dietary iron is absorbed (1–2 mg/day).

Absorption

- Iron is mainly absorbed in the duodenum and upper jejunum.
- A protein called divalent metal transporter 1 (DMT1) facilitates iron transfer across intestinal epithelial cells.
- Normally, individuals absorb less than 10% of dietary iron, or 1–2 mg per day balancing the daily loss from desquamation of epithelia.
- Most absorbed iron is used in bone marrow for erythropoiesis.
- Iron homeostasis is closely regulated via intestinal absorption.
- Once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss (i.e., pregnancy, menstruation or other bleeding.)
Transport

- Most absorbed iron is transported in the bloodstream bound to the glycoprotein transferrin.
- Transferrin is a carrier protein that plays a role in regulating the transport of iron from the site of absorption to virtually all tissues.
- Transferrin binds only two iron atoms.
- Normally, 20–45% of transferrin binding sites are filled (measured as percent transferrin saturation [TS]).

Normal Iron Absorption and Metabolism

![Diagram of iron absorption and metabolism]

Figure 1. Iron is bound and transported in the body via transferrin and stored in ferritin molecules. Once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss i.e., pregnancy, menstruation or other bleeding.

Use

- 75% of absorbed iron is bound to proteins such as haemoglobin that are involved in oxygen transport.
- About 10% to 20% of absorbed iron goes into a storage pool that is also recycled in erythropoiesis, so storage and use are balanced.

Storage

- Iron is initially stored in ferritin molecules.
- A single ferritin molecule can store up to 4,000 iron atoms.
- When excess dietary iron is absorbed, the body responds by producing more ferritin to facilitate iron storage.
Figure 2. Ferritin molecules store thousands of iron atoms within their mineral core. When excess dietary iron is absorbed, the body responds by producing more ferritin to facilitate iron storage.

**AETIOLOGY**

Iron deficiency can occur at any time during the prenatal period, due to one or more contributing factors. All risk factors should be assessed and the cumulative effect evaluated. Its has despite in Table 1: A summary of some risk factors contributing to iron deficiency and iron deficiency anemia.\(^\text{10}\)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet low in bio available iron (See Iron handout)</td>
<td>• Food choice and availability limited (See Iron handout)</td>
</tr>
<tr>
<td>• Low intake of:</td>
<td>• Diet restriction – Prescribed or self-imposed, i.e. vegan</td>
</tr>
<tr>
<td>• Iron rich foods</td>
<td>• Eating disorder</td>
</tr>
<tr>
<td>• Iron enhancers, – “helpers”</td>
<td>• Food insecurity</td>
</tr>
<tr>
<td>• High intake of:</td>
<td>• Lead exposure</td>
</tr>
<tr>
<td>• Iron inhibitors - “blockers”</td>
<td></td>
</tr>
<tr>
<td>• Presence of iron competitors</td>
<td></td>
</tr>
<tr>
<td>Rapid growth</td>
<td>• Adolescence</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy</td>
</tr>
<tr>
<td></td>
<td>• Increased blood volume</td>
</tr>
<tr>
<td></td>
<td>• Foetal and placental growth</td>
</tr>
<tr>
<td></td>
<td>• Other maternal tissues</td>
</tr>
<tr>
<td></td>
<td>• Multiple pregnancy</td>
</tr>
<tr>
<td>Blood loss</td>
<td>• Menstruation</td>
</tr>
<tr>
<td></td>
<td>• Gastrointestinal tract</td>
</tr>
<tr>
<td></td>
<td>• Food sensitivity</td>
</tr>
</tbody>
</table>
### Other factors

- High parity
- Racial group
- History of iron deficiency anaemia
- Pica *
- Impaired absorption
  - Intestinal malabsorption
  - Bariatric Surgery (weight-loss surgery)
- Hypochlorhydria
- Low socioeconomic status
- Recent immigrant
- Infection
- Hereditary medical disorders causing anaemia
- Extreme exercise

#### Postpartum

- Anaemia through the third trimester
- Excessive blood loss during delivery
- Multiple birth

*Women consuming non-food substances, containing or possibly containing lead require further evaluation prior to commencing iron supplementation.*

**SIGNS AND SYMPTOMS**

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Pallor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethargy</td>
<td>Flattened, brittle nails (spoon nail shown in Figure:3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Angular stomatitis (cracks at mouth corners)</td>
</tr>
<tr>
<td>Headaches</td>
<td>Glossitis</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Blue sclera (whites of eyes)</td>
</tr>
<tr>
<td>Ringing in ears</td>
<td>Pale conjunctivae</td>
</tr>
<tr>
<td>Taste disturbances</td>
<td>Pica (ice chewing)</td>
</tr>
<tr>
<td>Restless leg syndrome</td>
<td></td>
</tr>
</tbody>
</table>
LONG-TERM EXPOSURE OF IRON DEFICIENCY ANEMIA

ID is a systemic condition impairing physical endurance, work capacity, infant growth and development, and depressing immune function. Among these conditions, the association between ID and child development has evoked the most attention among researchers. Decreased brain iron stores may impair the activity of iron-dependent enzymes necessary for the synthesis, function and degradation of neurotransmitters, such as dopamine, serotonin and nor-adrenaline, causing changes in behaviour and lowering of development test scores in children. Several extensive reviews have been published on the association between IDA and child development. A review by Martins S et al., have clearly reported that IDA does expose children to concurrent and future risk of poor development. Whether this condition is reversible by treatment of iron has been inconclusive. Of six randomized controlled trials in children less than two years old, only one showed a significant impact. Of eight double-blind, randomized controlled trials of iron therapy in children older than two years, four reported significant outcome. This indicates that either the impact of ID is irreversible or there are other factors associated with this condition.

NUTRITIONAL ASSESSMENT

- Biochemical data
  - Hemoglobin or hematocrit
  - Mean cell volume, red blood cell distribution, width
  - Serum ferritin concentration
Clinical factors

- Age
- Reproductive status
- Prescribed medication and/or over the counter supplements
- Multiple / Prenatal vitamins and minerals
- Iron
- Calcium
- Antacids

Risk factors for iron deficiency – see Table 1

Dietary practices and patterns

- Increase and optimize intake of iron-rich foods and foods that enhance iron absorption (See iron handout for further guidelines)

Table 2. List of biochemical tests for Iron Deficiency Anaemia

<table>
<thead>
<tr>
<th>S.No</th>
<th>Method</th>
<th>Manufacturer’s normal value</th>
<th>Iron deficiency criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>IRON liquicolor photometric colorimetric test for iron with lipid clearing</td>
<td>Men 59–148 µg/dL Women 37–145 µg/dL</td>
<td>Men &lt; 59 µg/dL Women &lt; 37 µg/dL</td>
</tr>
<tr>
<td>Total iron-binding capacity (TIBC)</td>
<td>TIBC test, iron saturation and aluminum oxide absorption method, human</td>
<td>250–370 µg/dL</td>
<td>&gt;370 µg/dL</td>
</tr>
<tr>
<td>Ferritin (Ferr)</td>
<td>Electrochemiluminescence immunoassay. Roche, Elecsys 2010/modular analytics</td>
<td>30–300 µg/mL</td>
<td>&lt;30 µg/mL</td>
</tr>
<tr>
<td>Transferrin saturation (% Tsat)</td>
<td>TIBC test/iron liquicolor, human</td>
<td>20%–45% ref</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Soluble transferrin</td>
<td>Enzyme-linked Quantikine IVD human sTfR immunoassay</td>
<td>8.7–28.1 nmol/L</td>
<td>&gt;28.1 nmol/L</td>
</tr>
<tr>
<td>receptor (sTfR)</td>
<td>MCV</td>
<td>SYSMEX. XE-alphaN automated hematology system roche,</td>
<td>80-90fL</td>
</tr>
<tr>
<td>---------------</td>
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<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>CHCM</td>
<td>SYSMEX. XE-alphaN automated hematology system roche,</td>
<td>32-36 µg/dL</td>
<td>≤32 µg/dL</td>
</tr>
</tbody>
</table>

A. Anemia

B. Normal blood

Figure: 4 Diagnosis of IDA

A > Showing hypochromic microcytic anemia of iron deficiency (Peripheral blood smear). Note the small red cells containing a narrow rim of peripheral hemoglobin. Scattered fully hemoglobinised cells, present due to recent blood transfusion, stand in contrast.

B > Showing normal blood cells.

Newer Techniques

Reticulocytic haemoglobin content

Erythrocyte and reticulocyte indices were measured with an automated hematology analyzer (ADVIA 120, Bayer Diagnostics, Tarrytown, NY), which quantifies mean values and distributions for cell volume, haemoglobin concentration, and haemoglobin content in both erythrocytes and reticulocytes. Serum iron and total iron-binding capacity (based on a transferrin immunoassay) were measured using a chemistry analyzer (Hitachi 917, Roche Diagnostics, Indianapolis, Ind). C-reactive protein was measured on a BNII nephelometer (Dade-Behring Inc, Deerfield, Ill). Zinc protoporphyrin was measured in whole blood with a hematofluorometer (Aviv Biomedical, Lakewood, NJ) and expressed as μmol/mol of heme.

PREVENTION

The problem of IDA can be addressed through primary prevention efforts or through the secondary prevention efforts of early detection and subsequent therapy. Primary prevention
has the potential of providing benefit to a whole population and preventing the onset of IDA. Primary prevention of IDA in infants and preschool children to be achieved through various dietary interventions, including breastfeeding and fortification of formula (if not breast-fed) or infant cereal. These interventions are only effective, when they are available and affordable for all children.  

**Dietary Factors that Enhance and Inhibit Iron Absorption**

Dietary iron sources include meat, fish and poultry, lentils, dried beans, grain products, vegetables, dried fruit, and molasses. Sources of heme iron from hemoglobin and myoglobin found in meat, fish, and poultry are effectively absorbed by receptors in the gut, while the bioavailability of non-heme iron from plants is determined by the presence of dietary factors that enhance or inhibit its absorption. 

<table>
<thead>
<tr>
<th>Enhance</th>
<th>Inhibit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>Phosphate</td>
</tr>
<tr>
<td>Fish</td>
<td>Calcium</td>
</tr>
<tr>
<td>Poultry</td>
<td>Tea (tannic acid)</td>
</tr>
<tr>
<td>Seafood</td>
<td>Coffee</td>
</tr>
<tr>
<td>Gastric acid</td>
<td>Colas</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Soy protein</td>
</tr>
<tr>
<td>Malic acid</td>
<td>High doses of minerals</td>
</tr>
<tr>
<td>Citric acid</td>
<td>Bran (hard outer layer of grain)/fiber</td>
</tr>
</tbody>
</table>

**TREATMENT**

Table 3. Provide oral formulations for adults
<table>
<thead>
<tr>
<th>Name of preparation (company)</th>
<th>Formulation</th>
<th>Elemental iron content</th>
<th>Other active ingredients</th>
<th>Mechanism of action</th>
<th>Contraindication</th>
<th>Adverse reaction</th>
<th>Drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FERRO-GRADUM (Abbott Australia) ET</td>
<td>Ferrous sulfate 325mg Controlled-release tablets</td>
<td>105mg</td>
<td>Nil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FERROGRAD C (Abbott Australia)</td>
<td>Ferrous sulfate 325mg Controlled-release tablets</td>
<td>105mg</td>
<td>Vitamin C 500mg</td>
<td>Replaces iron found in haemoglobin, myoglobin, other enzymes and allow the transportation of oxygen via HB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGF (Abbott Australia)</td>
<td>Ferrous sulfate 250mg Controlled-release tablets</td>
<td>80mg</td>
<td>Folic acid 300 g</td>
<td></td>
<td>Haemolytic anemia, Hypersensitive to iron salts.</td>
<td>&gt;10% - Gastro Intestinal irritation, epigastric pain.</td>
<td></td>
</tr>
<tr>
<td>FEFOL iron and folate supplement (Pharmacare Laboratories)</td>
<td>Ferrous sulfate 270mg Controlled-release capsules</td>
<td>87mg</td>
<td>Folic acid 300 g</td>
<td></td>
<td></td>
<td>1-10% - Heartburn, Diarrhoea</td>
<td>Increase effect- Discolouration of urine, ≥ 200mg Vitamin-C per 30mg increases iron absorption. Decrease effect- In combination with antacids, H2 blockers (Cimetidine/PPI) decrease iron absorption.</td>
</tr>
<tr>
<td>FERRO-F-TAB (AFT Pharmaceuticals)</td>
<td>Ferrous fumarate 310mg Non-controlled-release tablets</td>
<td>100mg</td>
<td>Folic acid 350 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Details of oral formulation for paediatrics (Children)

<table>
<thead>
<tr>
<th>Name of preparation (company)</th>
<th>Formulation</th>
<th>Elemental iron content</th>
<th>Mechanism of action</th>
<th>Contraindication</th>
<th>Adverse reaction</th>
<th>Drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FERRO-LIQUID (AFT Pharmaceuticals)</td>
<td>Ferrous sulphate Oral liquid 150mg/5ml</td>
<td>30mg/5 ml</td>
<td>Replaces iron found in haemoglobin, myoglobin, other enzymes and allow the transportation of oxygen via Hb.</td>
<td>Haemolytic anemia, Hypersensitive to iron salts</td>
<td>&gt;10% - Gastro Intestinal irritation, Epigastric pain. 1-10% - Heartburn, Diarrhoea.</td>
<td>Increase effect- Discolouration of urine, ≥ 200mg Vitamin-C per 30mg increases iron absorption. Decrease effect- In combination with antacids, H₂ blockers (Cimetidine /PPI) decrease iron absorption.</td>
</tr>
</tbody>
</table>
MAJOR REASONS FOR INADEQUATE RESPONSE TO ORAL IRON THERAPY

- Inadequate iron intake
  - Patient not taking oral iron therapy
  - Patient taking an iron supplement or multivitamin tablet with insufficient iron content

- Inadequate iron absorption
  - Concomitant consumption of inhibitors of iron absorption (eg, tea, calcium, antacids, tetracycline, within 2 hours of iron ingestion)
  - Coexisting inflammation with functional iron deficiency
  - Intestinal mucosal disorders (eg: Coeliac disease, inflammatory bowel disease)
  - Impaired gastric acid secretion (including use of proton pump inhibitors)
  - Gastric/intestinal bypass procedures
  - Helicobacter pylori colonization
  - Controlled-release iron formulations may contribute (ie, potential for limited iron absorption in some patients)†

- Ongoing iron losses or need in excess of dose absorbed:
  - Occult, undiagnosed or recurrent gastrointestinal blood loss (eg, peptic ulcer, malignancy, angiodysplasia, small bowel lesion, parasites)
  - Other source of recurrent blood loss (eg, menorrhagia due to Uterine pathology or an inherited bleeding disorder such as von Willebrand disorder)
  - Multiple sources of recurrent blood loss (eg, hereditary haemorrhagic telangiectasia)
  - Ongoing urinary iron losses (eg, significant valve haemolysis)
  - Renal failure responding to erythropoietin-stimulating agents

- Coexisting condition interfering with bone marrow response
  - Superimposed infection, inflammation, malignancy or renal failure
  - Concomitant B12 or folate deficiency
  - Coexisting primary bone marrow disease or suppression

- Incorrect diagnosis or more than one cause of anaemia
  - Anaemia of chronic disease or renal failure
- Haemoglobinopathy
- Other causes of anaemia (eg, haemolysis, myelodysplastic syndromes, congenital anaemia, endocrine disorders)

*More than one factor is often present. † Role is unclear (limited available data show efficacy comparable to that of non-controlled-release formulations).

### Table 5: Details of intravenous formulations

<table>
<thead>
<tr>
<th>Name of preparation (company)</th>
<th>Formulation</th>
<th>Elemental iron content</th>
</tr>
</thead>
<tbody>
<tr>
<td>FERRUM H (Aspen Pharmacare)</td>
<td>Iron polymaltose</td>
<td>100mg ampoules</td>
</tr>
<tr>
<td>FERROSIG (Sigma Pharmaceuticals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VENOFER‡‡ (Aspen Pharmacare)</td>
<td>Iron sucrose</td>
<td>100mg ampoules</td>
</tr>
</tbody>
</table>

‡‡ Use intermittent small doses (NOT suitable for a total-dose infusion in one treatment); currently only funded by Pharmaceutical Benefits Scheme for specific indications in chronic kidney disease.

**MANAGEMENT**

Preschool children
- Consider:
  - Inadequate dietary iron
  - Inadequate complementary foods
  - Cow’s milk allergy
  - Rapidly-rebound growth, former low birth weight
  - Coeliac disease
  - Parasitic infection
  - GI blood loss

- Treatment:
  - Oral iron liquid (3–6 mg/kg elemental iron per day) for at least 2–3 months after normalization of Hb
  - Optimise dietary iron content

Older children
- Consider:
  - Inadequate dietary iron (especially if vegetarian)
  - Rapidly-rebound growth
  - Coeliac disease
  - Parasitic infection
  - GI blood loss

- Treatment:
  - Oral iron (usually 100–200 mg elemental iron per day) for at least 3 months after normalization of Hb
  - IV iron for selected patients – Pregnancy, non compliance
  - Optimise dietary iron (secondary prevention) and address underlying cause

Adolescent and premenopausal women
- Consider:
  - Inadequate iron intake
  - Blood loss (e.g., menorrhagia, GI haemorrhagic defect)
  - Coeliac disease
  - Parasitic infection
  - GI blood loss

- Risk factors for GI pathology:
  - GI symptoms
  - Family history of colorectal cancer
  - Age ≥ 50 years
  - Refractory, recurrent or unexplained IDA

- Treatment:
  - GI blood loss (e.g., neoplasia)
  - Coeliac disease investigations
  - Gastroscopy/colonoscopy
  - Others as directed by clinical findings and content

Adult men and postmenopausal women
- Consider:
  - Inadequate iron intake
  - Blood loss (e.g., menorrhagia, GI haemorrhagic defect)
  - Coeliac disease
  - Parasitic infection
  - GI blood loss

- Treatment:
  - Oral iron (usually 100–200 mg elemental iron per day) for at least 3 months after normalization of Hb
  - IV iron for selected patients – Pregnancy, non compliance
  - Optimise dietary iron (secondary prevention) and address underlying cause
CONCLUSION

IDA in children remains a public health problem, and children are at particularly high risk. IDA is associated with poor developmental outcomes in children; the impact of ID is less well understood. Laboratory investigations include haemoglobin and iron tests, such as serum ferritin. Primary prevention of IDA is recommended; the role of secondary prevention through screening programs remains inconclusive but recommended by some professional organizations. Treatment of children identified with IDA includes both dietary counselling and oral iron supplementation. ID can occur without the presence of anaemia, and also capable of causing developmental delay in children remains controversial. Only one study has demonstrated a significant effect of iron supplementation in these children. Further studies are needed to fully understand the effectiveness of oral iron treatment for children with only ID.

REFERENCES


