Iron Deficiency and Anemia
Causes, Consequences, and Solutions

Parul Christian
International Nutrition
2005
Outline

• Anemia, ID, IDA – Global burden
• Iron requirements
• Etiology of IDA
• Functional and health consequences of ID and anemia
• Iron-infection interaction
• Strategies for combating iron deficiency and anemia
Biologic Importance of Iron

- Iron is essential for almost all living organisms
  - Participates in oxidative and reductive processes as part of redox enzymes and thus plays an essential role in oxidative energy production
  - Involved in oxygen transport as part of the heme molecule
Iron deficiency

• Importance

Iron deficiency is the most prevalent nutritional deficiency in the world, and probably the most important micronutrient deficiency in the US. Globally, it is estimated to affect 1.25 billion people.
Iron deficiency vs. anemia

Diagram:
- Anemia
- IDA
- Iron deficiency
- Iron
FIGURE 2.1: Prevalence of anaemia by age group in industrialized and developing countries, 1998

Percent

0–4 years  5–14 years  Nonpregnant women  Pregnant women  Men  Elderly

■ Developing countries □ Industrialized countries
FIGURE 2.2: Prevalence of anaemia in children 0–5 years old by WHO region, 1998
Heme Molecule
## Iron compounds
(approx. values for a 55 kg woman)

<table>
<thead>
<tr>
<th>Functional Compounds</th>
<th>Hemoglobin</th>
<th>1700 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myoglobin</td>
<td>222 mg</td>
</tr>
<tr>
<td></td>
<td>Heme enzymes</td>
<td>50 mg</td>
</tr>
<tr>
<td></td>
<td>Non-heme enzymes</td>
<td>55 mg</td>
</tr>
<tr>
<td></td>
<td>Transferrin</td>
<td>3 mg</td>
</tr>
<tr>
<td>Storage Complexes</td>
<td>Ferritin</td>
<td>200 mg</td>
</tr>
<tr>
<td></td>
<td>Hemosiderin</td>
<td>70 mg</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2300 mg</td>
</tr>
</tbody>
</table>
Comparison of screening and definitive measurements of iron status

<table>
<thead>
<tr>
<th>Screening</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemoglobin</td>
<td>Inexpensive, Universally available</td>
<td>Low sensitivity, Low specificity</td>
</tr>
<tr>
<td>2. Transferrin saturation</td>
<td>Inexpensive, Well established</td>
<td>Wide diurnal variation, Low specificity</td>
</tr>
<tr>
<td>3. Mean corpuscular Hb</td>
<td>Well available, established</td>
<td>Late indicator, low specificity</td>
</tr>
<tr>
<td>4. Zinc protoporphyrin</td>
<td>Portable assay, Inexpensive</td>
<td>Automation difficult, Affected by lead exposure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definitive</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Serum ferritin</td>
<td>Quantitative (stores), well standardized</td>
<td>Affected by inflammation, liver disease</td>
</tr>
<tr>
<td>2. STfr</td>
<td>Quantitative (tissue deficiency) unaffected by inflammation</td>
<td>Affected by recombinant human erythropoietin</td>
</tr>
<tr>
<td>3. Bone-marrow iron</td>
<td>Well established, high specificity</td>
<td>Affected by EPO treatment, invasive, expensive, error-prone</td>
</tr>
</tbody>
</table>

Cook JD; Best Pract Res Clin Haematol 2005
Quantitative assessment of body iron

Body iron (mg/kg) =
-\[\log (R/F \text{ ratio}) - 2.8229]/0.1207

R = transferrin receptor
F = ferritin

Cook JD; Blood 2003
### Defining anemia at sea level

<table>
<thead>
<tr>
<th>Age or Sex group</th>
<th>Hb below g/dL</th>
<th>Hematocrit below %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6mo-5 y</td>
<td>11.0</td>
<td>33</td>
</tr>
<tr>
<td>Children 5-11 y</td>
<td>11.5</td>
<td>34</td>
</tr>
<tr>
<td>Children 12-13 y</td>
<td>12.0</td>
<td>36</td>
</tr>
<tr>
<td>Non-pregnant women</td>
<td>12.0</td>
<td>36</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>11.0</td>
<td>33</td>
</tr>
<tr>
<td>Men</td>
<td>13.0</td>
<td>39</td>
</tr>
</tbody>
</table>

Stoltzfus & Dreyfuss; INACG/UNICEF/WHO 1998
Dietary Iron

• Two types of iron
  – Heme iron (animal sources)
  – Non-heme iron (plant sources)
• Absorption of heme iron is 20-30%
• Absorption of non-heme iron varies between 1-10% and is much more affected by iron status and intraluminal factors
Non-heme Iron Absorption

- Enhancers: ascorbic acid, meat
- Inhibitors: phytates, phosphates, tannins, oxalates, soy protein
- Other nutrients: zinc, calcium
# Iron requirements for growth

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (y)</th>
<th>Wt gain (kg)</th>
<th>Mg iron/kg body wt</th>
<th>Mean iron for growth (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>0.25-1</td>
<td>4.2</td>
<td>37</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>2.4</td>
<td>37</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>2-6</td>
<td>7.9</td>
<td>40</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>6-12</td>
<td>20.2</td>
<td>41</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>12-16</td>
<td>26.2</td>
<td>46</td>
<td>0.66</td>
</tr>
<tr>
<td>Boys</td>
<td>12-16</td>
<td>15.2</td>
<td>43</td>
<td>0.36</td>
</tr>
<tr>
<td>Girls</td>
<td>12-16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Iron Losses
### Men and Post-menopausal Women

<table>
<thead>
<tr>
<th>Area of loss</th>
<th>Amount (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feces</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Urine</td>
<td>0.2-0.3</td>
</tr>
<tr>
<td>Sweat, hair, nails</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.8-1.0</strong></td>
</tr>
</tbody>
</table>
### Iron Losses
(Menstruating women - 55 kg)

- Additional loss of 0.5 mg/d of Fe occurs due to menstruation; range is high

<table>
<thead>
<tr>
<th></th>
<th>Basal Fe loss</th>
<th>Menstrual Fe loss</th>
<th>Total Fe loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>No contraceptive</td>
<td>14</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>14</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>IUD</td>
<td>14</td>
<td>16</td>
<td>30</td>
</tr>
</tbody>
</table>
Causes of anemia

• Major causes
  – Iron deficiency (1300-2200 m)
  – Hookworm (876 m)
  – Vitamin A deficiency (300 m)
  – Malaria infection (300 m)

• Other Important causes
  – Chronic infections: TB, HIV
  – Other vitamins
  – Genetic defects
Hookworm and Malaria in the Etiology of Iron Deficiency and Anemia

Proportion of Zanzibari children with severe anemia (hemoglobin <80 g/L) by malaria parasite density or hookworm fecal egg counts and age group. Chi-square tests for trends of association: malaria parasite density in age <30 months, P<0.00001, age ≥ 30 months, P>0.20. Hookworm fecal egg counts in age <30 months, P = 0.002, age ≥30, P = 0.005.

Adapted from: Stoltzfus et al, J Nutr 2000
Hookworm and Malaria in the Etiology of Iron Deficiency and Anemia

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Adapted from: Stoltzfus et al, J Nutr 2000
Etiologies of anemia in pregnant rural Nepali women

Dreyfuss et al, J Nutr 2000
Deficiency of vitamins may cause anemia

- RBC production (erythropoiesis)
- Protect mature RBC free radical oxidation
- Fe mobilization
- Fe absorption

- VA, FA, B12, B6, riboflavin
- VC, VE
- VA, VC, riboflavin

Fishman, Christian and West et al, PHN 2000
Vitamin A and iron interaction in Indonesian pregnant women

Suharno et al, AJCN 1993
Iron and micronutrients supplementation in anemic Mexican children - RCT

(Lopez et al, J Nutr 2001)

Change in Hb (g/L)

Placebo  Fe  Fe+B12  Fe+MN

B2, B12, A, B6, E, folic acid, zinc, copper
Impact of antenatal multiple micronutrient supplementation on anemia in the third trimester

Christian et al, J Nutr 2003; Ramakrishnan et al, J Nutr 2004
Consequences of Iron Deficiency and Anemia

- Decreased work capacity
- Prematurity and LBW
- Perinatal mortality
- Maternal mortality
- Child mortality
- Impaired neurocognitive function in children
Iron and work capacity

Iron deficiency

IDA

Anemia

Tissue Oxidative Capacity

Oxygen Carrying Capacity

Work capacity
Energetic efficiency
Endurance
VO_{2}\text{max}
Iron deficiency and anemia and work capacity

- Laboratory studies
  - IDA causally associated with 10-50% reduction in VO$_2$ max
  - No clear association between IDA and endurance capacity
  - ID may impair energetic efficiency

- Field studies
  - Provide further causal evidence
  - ID and IDA may affect productivity
  - Institutional and technological factors may constrain ability or motivation of subjects
What does this mean?

- Productivity losses due to iron deficiency
- Losses to GNP estimated from 6 countries range from 0.85% to 1.27%
- South Asia, where ID is high, loses $5 billion annually
Consequences of Pregnancy Anemia

Maternal anemia (any cause) during pregnancy

Low birthweight

Preterm

FGR

Preterm and FGR

Perinatal death

Adapted from Rasmussen, J Nutr 2001
Fetal/Placental development

- Maternal hematocrit determines O₂ tension in amniotic fluid (Nigeria)
- Maternal anemia/iron status influences placental size, morphology
- ID may be associated with increases in maternal ACTH and cortisol
Incidence of low birth weight (<2500 g) by haemoglobin concentration (g/L).

*Data for white women only.*

Adapted from: Steer et al; BMJ 1995
Child Development

Incidence of preterm labor (<37 full weeks) by haemoglobin concentration (g/L) *Data for white women only.*

Adapted from: Steer et al; BMJ 1995
Antenatal iron and low birth weight

- All systematic reviews of RCTs have found evidence to be inconclusive (Rasmussen 2000)
  - Mainly because of poorly conducted studies, inadequate design, low sample size, biases
- Recent trials in Nepal and the US found that antenatal iron supplementation increased birth weight
Effect of antenatal iron supplementation on birth weight in rural Nepal

- Iron folate improved birth weight by about 80g for weights below 2800 g

Christian et al; unpublished
Anemia and maternal mortality

• No clinical trials, but strong clinical impression
• “At 6.0g/dL evidence of circulatory decompensation becomes apparent. Women experience breathlessness and increased cardiac output at rest. At this stage, added stress of labor can result in maternal death. Without effective treatment, maternal death from anemic heart failure is likely with Hb concentration of 4.0g/dL. Even a blood loss of 100 ml can cause circulatory shock and death.” (INACG Statement)
Child Mortality

• Relationship through infectious disease incidence is unlikely
• Relationship through anemia is possible, and probably severe anemia of any cause
Nepal Trial

- RCT, 2x2 factorial design
- Placebo, Fe+FA, Zn, Fe+FA+Zn
- Children ages 2-35 mo
- Outcome: Infant/Child survival
- Iron arms of the trial stopped because of a lack of any impact on infant/child survival

Tielsch et al; unpublished
Child Development

• **Iron** may affect brain development through decreased brain iron which affects
  – Myelination
  – Neural transmission systems (both neuronal metabolism and dopaminergic functioning)

• Functions affected
  – Delays in maturation of visual, auditory, motor functions and other aspects of neurofunctional development (e.g. recognition memory)
  – Child-caregiver interaction
  – Child “functional isolation” through lack of exploratory movement
Iron status and neurocognitive development

Modified from Pollit E; EJCN 2000
Child Development

Long-term Outcome of Infants with Iron Deficiency

Adapted from Lozoff et al; NEJM 1991
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Final language score*</th>
<th>Difference in score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=85)</td>
<td>13.1 (12.7 to 13.9)</td>
<td></td>
</tr>
<tr>
<td>Mebendazole (n=85)</td>
<td>13.5 (12.6 to 14.4)</td>
<td></td>
</tr>
<tr>
<td>Iron (n=94)</td>
<td>14.0 (13.2 to 14.8)</td>
<td></td>
</tr>
<tr>
<td>Mb + iron (n=85)</td>
<td>14.2 (13.4 to 15.0)</td>
<td></td>
</tr>
<tr>
<td>Effect of iron v no iron</td>
<td></td>
<td>0.8 (0.2 to 1.4)</td>
</tr>
<tr>
<td>Effect of Mb vs no Mb</td>
<td></td>
<td>0.3 (−0.3 to 0.9)</td>
</tr>
</tbody>
</table>

Stoltzfus et al; BMJ 2001
Child Development - Summary

• Evidence favors a true relationship, but not conclusive; data from RCTs are not consistent
• Issues of timing, reversibility and optimal intervention remain unresolved
• Predictive and construct validity of Bayley’s scales is questionable
Tissue Iron Deficiency

Severe Anemia

- Work performance
- Work performance
- Child mortality
- Maternal mortality
- Perinatal mortality

Other Factors

Adapted from: Stoltzfus RJ; J Nutr 2001
Iron Supplementation and Infectious Disease

• 3 Systematic reviews:
  – Shankar et al (iron supplementation and malaria)
  – Oppenheimer (all interventions, all ages, all outcomes)
  – Gera and Sachdev (iron supplementation and incidence of infections in children)
INACG Consensus Statement-1999 (based on Shankar et al.)

• “Known benefits of iron supplementation are likely to outweigh the risk of adverse effects caused by malaria…Oral iron supplementation should continue to be recommended in malarious areas where IDA is prevalent”.
Belmont meeting* conclusion (based on Oppenheimer)

- Evidence not convincing for or against a relationship of public health significance

* WHO/INACG convened meeting

Oppenheimer SJ; J Nutr 2001
Iron supplementation in young children in Pemba, Zanzibar

- 2x2 factorial study of iron-folic acid and zinc in malaria endemic Pemba island
- The iron arms of the trial were discontinued due to evidence of increased hospitalization and mortality
- In a subsample, where children received treatment for malaria and other infections, iron reduced mortality in iron deficient children

Sazawal, Black, Unpublished
Infectious disease and iron supplementation - summary

• IF an adverse relationship exists, it probably derives from risks of iron intervention, not protective effect of iron
• THUS, question is NOT: Is it better for children to be iron deficient
• BUT RATHER: How can we safely correct iron deficiency?
• Pemba study suggests screening and treatment of malaria and other infections may be required
Prevention and treatment guidelines for iron supplementation (WHO/UNICEF/INACG)

- Pregnant women:
  - **Prevention**: 60 mg iron + 400 µg folic acid daily for 6 mo in pregnancy
  - **Treatment of severe anemia**: 120 mg iron + 400 µg folic acid daily for 3 mo
- Children 6-24 mo:
  - **Prevention**: 12.5 mg iron + 50 µg folic acid daily from 6-12 mo of age or from 2-24 mo of age if lbw
  - **Treatment of severe anemia**: 25 mg iron + 100-400 µg of folic acid daily for 3 mo
- Children 2-5 yr: 20-30 mg iron
- Where hookworm is endemic, give anthelminthics
Prevention Strategies

• Supplementation of target populations – little success in pregnancy
• Dietary diversification/modification – can it work?
• Fortification – Potential vehicles: cereals, flour, condiments, infant formula. Issues regarding the appropriate vehicle, type of fortificant, organoleptic properties, bioavailability, efficacy and effectiveness
<table>
<thead>
<tr>
<th>Aim</th>
<th>Whom to Supplement</th>
<th>Programmatic Implications</th>
<th>How to Evaluate Aim</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reach full Hb potential (prevent and treat)</td>
<td>All</td>
<td>Routine supplementation of all women</td>
<td>All who may benefit receive supplement</td>
<td>High effectiveness</td>
<td>Uncertainty of cut-off levels, difficulties in screening?</td>
</tr>
<tr>
<td>Prevent low Hb level</td>
<td>Those at risk for low Hb level</td>
<td>Routine or screening</td>
<td>% above low Hb level</td>
<td>Moderate effectiveness</td>
<td>Uncertainty of cut-off levels, difficulties in screening?</td>
</tr>
<tr>
<td>Treat low Hb level</td>
<td>Those below low Hb level</td>
<td>Screening low level</td>
<td>% above low Hb level</td>
<td>High effectiveness</td>
<td>Uncertainty of cut-off levels, difficulties in screening?</td>
</tr>
</tbody>
</table>

## Difficulties in Iron Supplementation

<table>
<thead>
<tr>
<th></th>
<th>Thailand</th>
<th>India</th>
<th>Indonesia</th>
<th>Myanmar</th>
<th>Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Service Utilization</td>
<td>***</td>
<td>*****</td>
<td>**</td>
<td>***</td>
<td>*</td>
</tr>
<tr>
<td>Tablet supply</td>
<td>***</td>
<td>***</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Within-facility factors</td>
<td>**</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Individual compliance</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

**** major constraint    * minor constraint
Effectiveness of iron-fortification
Iron coated-rice among Philippino children

Mannar & Gallego, J Nutr 2002
Effectiveness of iron-fortification

Iron-fortified fish sauce in Vietnam

Mannar & Gallego, J Nutr 2002
Special case - Infants

- Infants are born with high iron stores
- Human milk has low iron content but bioavailability is high
- First 2-3 mo of life: exclusively BF infant is in positive iron balance
- During 3-6 mo of life infants are in negative balance
- Foods with bioavailable iron, fortified foods or a low-dose iron supplement should be provided at 6 mo (IOM recommendation)
Prevalence of IDA among 8-mo old infants

Walter et al, Pediatrics 1993
Home-fortification or Sprinkles

• “Sprinkles” are single-dose sachets containing micronutrients in a powdered form, which are easily sprinkled onto any foods prepared in the household.
• Great for adding to complementary foods for young children.
• Any homemade food can be fortified with the single-dose sachets, hence the term “home fortification”.
• Sprinkles Nutritional Anemia Formulation has been tested in infants.
Effective control of anemia through combination of strategies

- Increased iron intake
  - Iron supplementation
  - Fortification of foods with iron (especially weaning foods)
- Control of parasitic infections (diagnosis and treatment, chemoprophylaxis, preventing transmission)
- Increased intake of other vitamins such as vitamin A, folic acid through
  - Supplementation, Fortification, Nutrition Education
Summary

• Causes of iron deficiency and anemia are multifactorial
• The strength of causal evidence that ID or anemia affects functional outcomes is variable
• Control of iron deficiency and anemia may require multiple strategies and is context specific