Iron Deficiency in the Global Context

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Iron Deficiency & Anemia

- Iron deficiency is the most prevalent nutritional deficiency in the world, estimated to affect 1.25 billion people
- Probably the most important micronutrient deficiency in the United States
- Iron is essential to every tissue in the body
- Basic biochemical function: give and receive electrons as it shifts between Fe++ and Fe+++ states
- Iron deficiency is strongly associated with anemia, but the two are distinct

Tissue Iron Deficiency:
- muscles, brain, etc.

Anemia:
- Deficiency of red cells

http://www.cdc.gov/ncbddd/hemochromatosis/training/pathophysiology/iron_cycle_popup.htm

Iron Deficiency Anemia (50%)

Anemia:
- Deficiency of red cells
  - (Low Hemoglobin)
Definitions of Anemia based on hemoglobin concentration (WHO, CDC)

<table>
<thead>
<tr>
<th>Age or sex group</th>
<th>Hemoglobin level (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHILDREN</td>
<td></td>
</tr>
<tr>
<td>6 months to 2 years</td>
<td>9.0</td>
</tr>
<tr>
<td>2 to 11 years</td>
<td>11.5</td>
</tr>
<tr>
<td>12 to 14 years</td>
<td>12.0</td>
</tr>
<tr>
<td>Men &gt; 15 years</td>
<td>13.0</td>
</tr>
</tbody>
</table>

To diagnose iron deficiency, you must also assess a more iron-specific biomarker. Common ones:
- Serum ferritin
- Serum transferrin receptor
- Zinc protoporphyrin

Anemia is extremely common: prevalence by global region, sex and age

<table>
<thead>
<tr>
<th>Region</th>
<th>0-4 y</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>E. Medit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S.A.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*excludes North America

Iron Deficiency & Anemia

**Tissue Iron Deficiency:** muscles, brain, etc.

**Anemia:** Deficiency of red cells

Why are young children and pregnant women so vulnerable to iron deficiency?

Because growing lean tissue and expanding blood volume consumes a lot of iron

Comparing iron requirements

<table>
<thead>
<tr>
<th></th>
<th>Man</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 kg</td>
<td></td>
<td>6 kg</td>
</tr>
</tbody>
</table>

Basal losses

Growth of lean tissues

Blood volume expansion

http://www.cdc.gov/nccdphp/dhdnp/training/pathophysiology/iron_cycle_popup.htm
Iron Requirement By Energy Intake

Infants require a very iron-dense diet, compared to adults.

Dietary Iron

- In most diets the problem is not the amount of iron, but the bioavailability.
- Bioavailability (%) is the proportion of the dietary iron that is actually absorbed into the body.

Dietary Iron

- Two types of dietary iron
  - Heme iron (animal sources)
  - Non-heme iron (non-animal sources)
- Absorption of heme iron is around 20-30% and is not influenced by other factors.
- Absorption of non-heme iron varies between 1-10%, and is much more affected by iron status and intraluminal factors.
- The strongest predictor of iron sufficiency in populations in meat intake.

Iron Enhancers and Inhibitors

- Enhancers:
  - Ascorbic acid
  - Red Meat: good source (heme) + enhancer
  - White Meats & Fish: enhancer
- Inhibitors:
  - Phytate (most important)
  - Tannins (tea)

- enhancers and inhibitors create up to 20-fold difference in fractional absorption (bioavailability).
Regulation of iron absorption

Three factors:
- Iron stores
- Erythropoiesis
- Inflammation

Too much iron is toxic. If iron absorption is not well regulated, the condition is eventually fatal.

Infants are a special case

- Infants are born with high iron stores (about 50% higher than the iron stores of an adult man, on a per kg basis)
- Estimated daily requirement is high
- Human milk iron content is low
- Thus babies depend on the stores they are born with
- Absorption and regulation of iron in young infants is not well understood; appears to be immature

Human milk is a sufficient source of iron for the first 6 months of life, but foods with bioavailable iron, iron-fortified foods or a low-dose iron supplement should be provided at 6 months or earlier, if supplementary foods are introduced before that time.

Iron Deficiency & Anemia

- Fetal growth
- Maternal iron status
- Cord clamping
- Bioavailable iron intake
- Infections, esp.
  - HIV
  - Malaria

Tissue Iron Deficiency:
- Anemia (50%)
- Muscles, brain, etc.

Easiest to measure

Anemia: Deficiency of red cells (Low Hemoglobin)
Increasing dietary iron

- Iron supplements
- Iron-rich additives to foods:
  - Sprinkles
  - Spreads
- Iron-fortified weaning foods
- Dietary modification:
  - Meat!

Comparing iron requirements

Iron Requirement By Energy Intake

The high physiological requirement for iron in pregnancy is difficult to meet with most diets. Therefore, pregnant women should routinely receive iron supplements in almost all contexts.

Hookworm: An additional consideration for older children and adults

- Hookworms live in the small intestine for about 3 years.
- They attach to the mucosa and consume constituents of blood.
- Blood loss due to GI bleeding is proportional to number of worms
- Effective deworming drugs are cheap and available, and safe to use in pregnancy (after 1st trimester)

Relation between hookworm infection and hemoglobin concentration
Part II: Consequences

- Child development
- Work productivity
- Economic development
- Infectious disease
- Pregnancy outcomes
- Maternal mortality

Child Development

- **Iron** may specifically affect brain development through:
  - myelination
  - neural transmission systems
- **Anemia** may affect through:
  - "functional isolation"; that is, adaptation to poor aerobic capacity and energetic inefficiency through lack of exploratory movement (*same as for PEM*)

Pemba Island

- Population approximately 300,000
- Infant Mortality Rate: 80/1,000
- *P. falciparum* holoendemic
- Staple foods: rice, cassava
- Soil-transmitted helminths endemic

Language Scale

18 items

1. Can say one word
5. If asked, can point to a dog
8. Uses the words: I, me, you
11. Can say many words (20 or more)
13. Can tell people his full name
15. Asks the meaning of words
18. Can tell me the opposite of "big"
Motor Scale
20 items

1. Crawl
4. Stand for a moment on her own
7. Run
10. Throw a ball overhand
13. Walk forward along a straight line
16. Walk on tiptoe
20. Hop 20 times on one leg

Baseline Associations (age-adjusted)

Percent time in locomotion: adjusted predicted values for Hb groups

Anemia Decreases Work Capacity in a laboratory test

And in the real world: Kenyan road workers
Not just aerobic labor:
iron effect on productivity of female cigarette rollers in Indonesia

<table>
<thead>
<tr>
<th></th>
<th>Multiple (n=100)</th>
<th>Iron (n=103)</th>
<th>Placebo (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 1</td>
<td>99.2</td>
<td>99.3</td>
<td>100.6</td>
</tr>
<tr>
<td>Wk 7</td>
<td>102.9</td>
<td>105.6</td>
<td>100.2</td>
</tr>
<tr>
<td>Wk 12</td>
<td>103.1</td>
<td>103.7</td>
<td>99.9</td>
</tr>
</tbody>
</table>

- Productivity expressed as % of average at different weeks during supplementation
- The cost of multi-supplementation per production line of 70 women is about $4 US
- The value of production increase is about $700 US
- Supplementation with iron would be cheaper than $1 US

What does this mean?

- Productivity losses due to Iron def:
  - Heavy labor, 17%
  - Blue collar labor, 5%
  - Cognitive losses from childhood, 4%
- Losses to GNP estimated from 6 countries range from 0.85% to 1.27%

From S. Horton, “The Economics of Nutritional Interventions” in Nutrition and Health in Developing Countries.

Iron and Infection

Optimal Iron Status

Relative risk of hospitalization associated with daily iron supplementation, by iron status category* at baseline

Zanzibar children, 1-35 mo, 2002-03

*Iron deficient defined as ZPP > 80 μmol/mol heme; Anemic defined as Hb < 10 g/dL

Micronutrient supplements and low birth weight in Nepal (Christian et al., 2003)

A new review based on 12 randomized trials found an average risk reduction of 19%. (Stoltzfus et al., forthcoming)
Follow-up of Nepalese babies to 7 years

Hazard ratio: 0.58 (0.3

Evidence suggests that the risk relationship is continuous

Estimated decrease in mortality risk for each 1 g/dL increase in pregnancy hemoglobin.

Iron-deficiency anemia an indirect cause of 20% of maternal deaths in childbirth

• Evidence suggests that the risk relationship is continuous
• Estimated decrease in mortality risk for each 1 g/dL increase in pregnancy hemoglobin.

Part III: Potential Solutions

• Targeted use of supplements:
  – To children at high risk of iron deficiency
  – To pregnant women
• Fortified foods
  – Staple foods reach whole population, but do not meet needs of infants
  – Foods designed for infants—requires food industry and affordable products
• Biofortification: use plant breeding to create better crop cultivars
  – Increase iron content
  – Decrease phytate content
• Hookworm control (sanitation, deworming drugs)
• Dietary strategies:
  – Increase meat consumption (expensive!)
  – Delayed cord clamping at delivery

Solutions with Proven Efficacy at Population Level

• Targeted use of supplements:
  – To children at high risk of iron deficiency—efficacious, but concern about infections
  – To pregnant women
• Fortified foods
  – Staple foods reach whole population, but do not meet needs of infants
  – Foods designed for infants—requires food industry and affordable products
• Hookworm control (sanitation, deworming drugs)
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Primary strategy: Antenatal Care

• Focused antenatal care: target number of ANC visits reduced to 4 (from 8-10):
  – 1st trimester, 24-28 wk, 32 wk, 36 wk
• Focused on:
  – Health promotion and disease prevention (includes reduction of iron deficiency anemia, and presumptive treatment for hookworm where prevalent)
  – Early detection and treatment of complications and existing diseases
  – Birth preparedness and complication readiness

How can iron supplements reach pregnant women?
How much time do health services spend on ANC? A recent study in Tanzania

Table 5. Comparison of current performance and anticipated standard of ANC counsel

<table>
<thead>
<tr>
<th>Activity</th>
<th>Current practice</th>
<th>Processed ANC</th>
<th>Current practice</th>
<th>Processed ANC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integration</td>
<td>0.93 min</td>
<td>0.15 min</td>
<td>0.93 min</td>
<td>0.15 min</td>
</tr>
<tr>
<td>History taking</td>
<td>0.12 min</td>
<td>0.05 min</td>
<td>0.12 min</td>
<td>0.05 min</td>
</tr>
<tr>
<td>Administration</td>
<td>0.01 min</td>
<td>0.00 min</td>
<td>0.01 min</td>
<td>0.00 min</td>
</tr>
<tr>
<td>Drug administration</td>
<td>0.01 min</td>
<td>0.00 min</td>
<td>0.01 min</td>
<td>0.00 min</td>
</tr>
<tr>
<td>Health education</td>
<td>0.03 min</td>
<td>0.00 min</td>
<td>0.03 min</td>
<td>0.00 min</td>
</tr>
<tr>
<td>Leaflet distribution</td>
<td>0.00 min</td>
<td>0.00 min</td>
<td>0.00 min</td>
<td>0.00 min</td>
</tr>
<tr>
<td>Measurement, 1st visit</td>
<td>0.20 min</td>
<td>0.03 min</td>
<td>0.15 min</td>
<td>0.02 min</td>
</tr>
<tr>
<td>Deceleration of findings</td>
<td>0.09 min</td>
<td>0.00 min</td>
<td>0.08 min</td>
<td>0.00 min</td>
</tr>
<tr>
<td>Total contact time</td>
<td>1.21 min</td>
<td>0.27 min</td>
<td>0.92 min</td>
<td>0.14 min</td>
</tr>
</tbody>
</table>

1 min 30 seconds for counseling/15 min needed

0 time for counseling

Tanzania needs: 78,300 health care workers to meet MDG targets
Tanzania has: 34,000

Micronutrients, including iron, included as part of larger child nutrition interventions

Infant and young child feeding (more to come on this . . . .)

The search for effective rice fortification

Three strategies being tried:
• Coat the rice kernels with fortificant
• Grind up the rice, mix in fortificant, reform into kernels
• Make a fake kernel that contains fortificant, mix into real kernels—most promising

Building healthy iron stores in the newborn infant

3 strategies:
• Adequate maternal iron status
• Prevent low birth weight
• Delay cord clamping
Building healthy iron stores in the newborn infant

Iron supplements to women and fortification strategies

3 strategies:
• Adequate maternal iron status
• Prevent low birth weight
• Delay cord clamping

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Delayed umbilical cord clamping increases newborn/infant iron status

• Delay of approximately 2-3 minutes allows a "placental transfusion" of 35-40 ml blood per kg body weight (term infants)
• For a 3.2 kg newborn, this amounts to 75 mg, or 3.5 mo of iron requirements (0.7 mg/day)

Source: van Rheenen, P. F et al. BMJ 2006;333:954-958
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