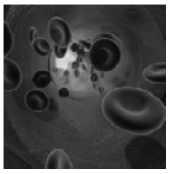


Iron Deficiency in the Global Context

Rebecca Stoltzfus, PhD

Division of Nutritional Sciences
Cornell University

September 20, 2011

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

Iron Deficiency & Anemia

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

Tissue Iron Deficiency:
muscles, brain, etc.

Easiest to Measure

Anemia:
Deficiency of red cells
(Low Hemoglobin)

Iron Deficiency & Anemia

Tissue Iron Deficiency:
muscles, brain, etc.

Iron Deficiency Anemia (50%)

Easiest to measure

Anemia:
Deficiency of red cells
(Low Hemoglobin)

Definitions of Anemia based on hemoglobin concentration (WHO, CDC)

Table 1. Hemoglobin cutoffs to define anemia in people living at sea level

Age or sex group	Hemoglobin below (g/L)
Children	
6 months to 5 years	110
5 to 11 years	115
12 to 14 years	120
Nonpregnant females > 15 years	120
Men >15 years	130

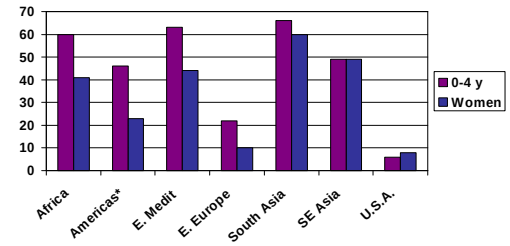
Table 2. Hemoglobin adjustment for pregnancy in women living at sea level

Stage of pregnancy (trimester)	Hemoglobin (g/L)
First	−10
Second	−15
Third	−10
Trimester unknown	−10

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



*excludes North America

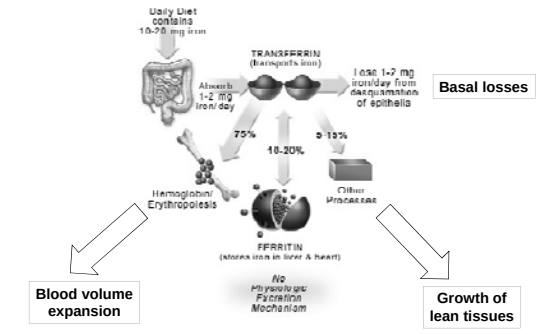
Iron Deficiency & Anemia

Tissue Iron Deficiency: muscles, brain, etc.

Anemia: Deficiency of red cells

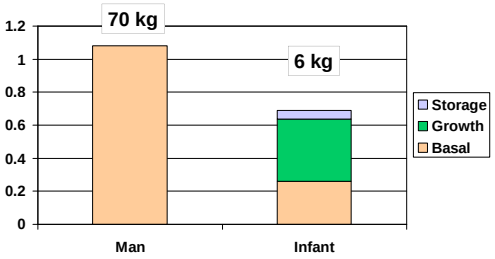
Why are young children and pregnant women so vulnerable to iron deficiency?

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

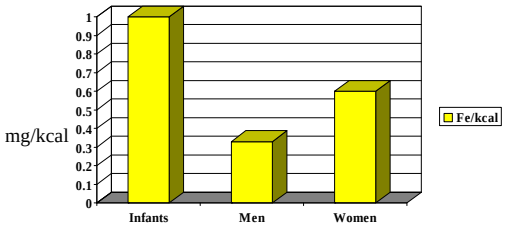


http://www.cdc.gov/ncbddd/hemochromatosis/training/pathophysiology/iron_cycle_popup.htm

Comparing iron requirements

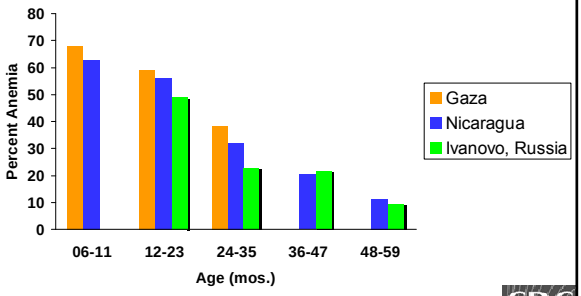


Iron Requirement By Energy Intake



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

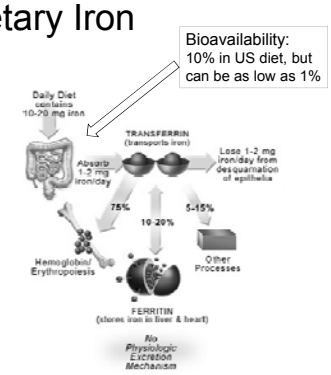
Children 6-24 months have highest risk of anemia



CDC

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

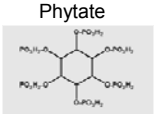
- Two types of dietary iron
  - heme iron (animal sources)
  - non-heme iron (non-animal sources)
- Absorption of heme iron is around 20-30% and is not influenced by other factors
- Absorption of non-heme iron varies between 1-10%, and is much more affected by iron status and intraluminal factors
- The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

Iron Enhancers and Inhibitors

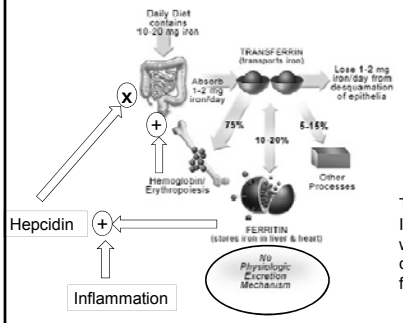
- Enhancers:
  - Ascorbic acid
  - Red Meat: good source (heme)+ enhancer
  - White Meats & Fish: enhancer
- Inhibitors:
  - Phytate (most important)
  - Tannins (tea)

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

Phytate



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.

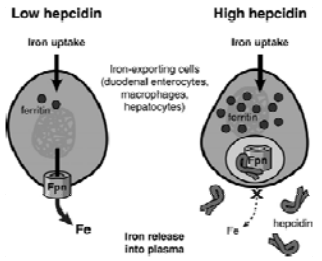


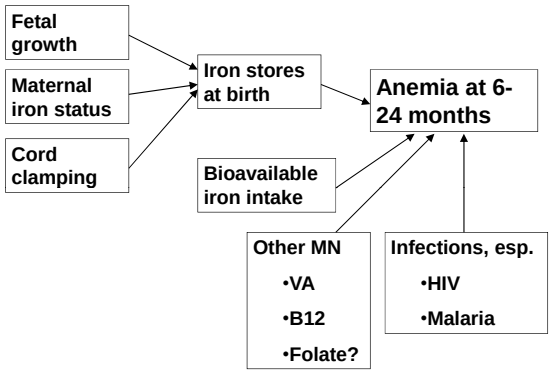
Figure 1. Hepcidin regulates cellular iron export into plasma. When hepcidin concentrations are low, ferroportin (Fpn) molecules are displayed on the plasma membrane and export iron. When hepcidin concentrations increase, hepcidin binds to ferroportin molecules and induces their internalization and degradation, and iron release is decreased progressively.

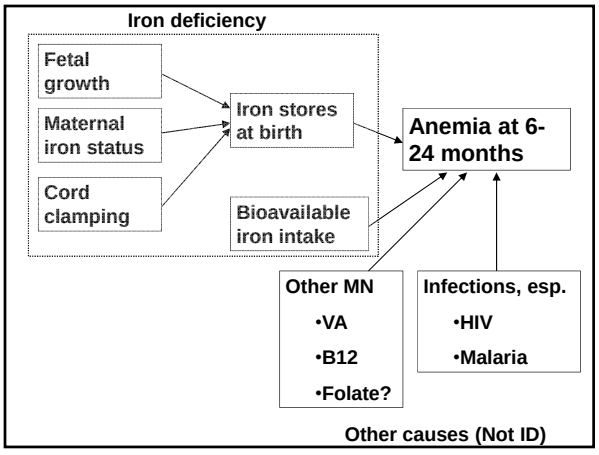
Ganz, T. J Am Soc Nephrol 18: 394-400, 2007

Infants are a special case

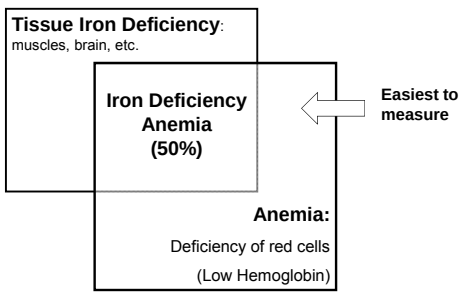
- Infants are born with high iron stores (about 50% higher than the iron stores of an adult man, on a per kg basis)
- Estimated daily requirement is high
- Human milk iron content is low
- Thus babies depend on the stores they are born with
- Absorption and regulation of iron in young infants is not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





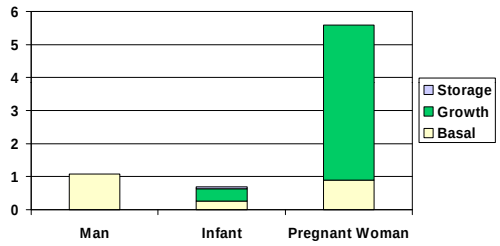
Iron Deficiency & Anemia



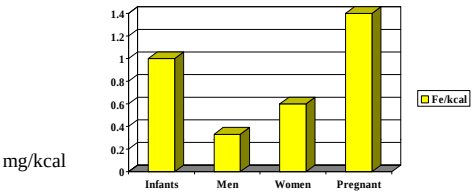
Increasing dietary iron

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

Comparing iron requirements



Iron Requirement By Energy Intake

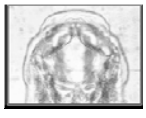


The high physiological requirement for iron in pregnancy is difficult to meet with most diets. Therefore, pregnant women should routinely receive iron supplements in almost all contexts.

Hookworm:

An additional consideration for older children and adults

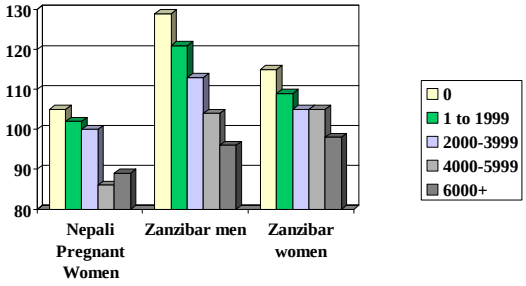
Ancylostoma duodenale



Necator americanus

- 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

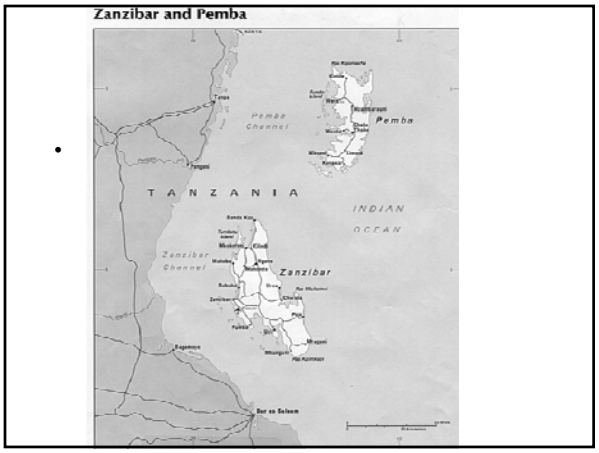
Economic

- Infectious disease
- Pregnancy outcomes
- Maternal mortality

Health

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)*



Language Scale

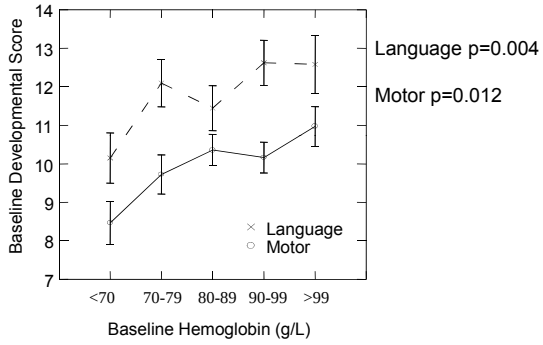
18 items

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"

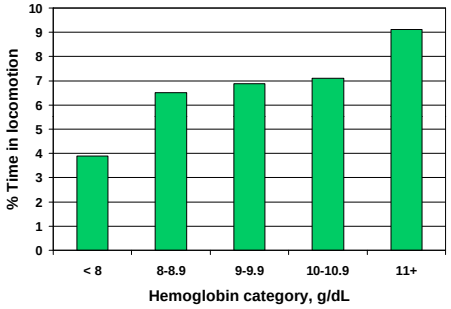
Motor Scale
20 items

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

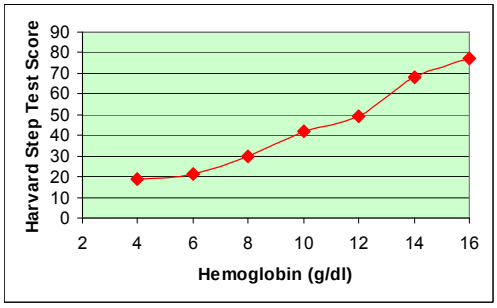
Baseline Associations (age-adjusted)



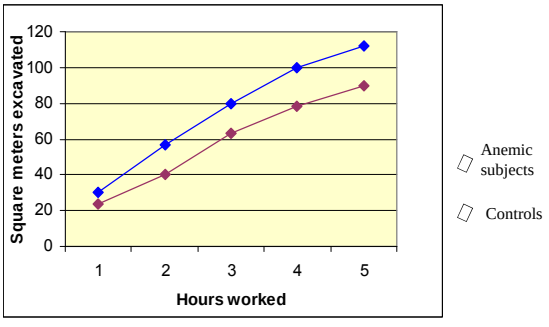
Percent time in locomotion: adjusted predicted values for Hb groups



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

	Multisup. (n=100)	Iron (n=103)	Placebo (n=105)
Wk 1	99.2	99.3	100.6
Wk 7	102.9	105.6	100.2
Wk 12	103.1	103.7	99.9

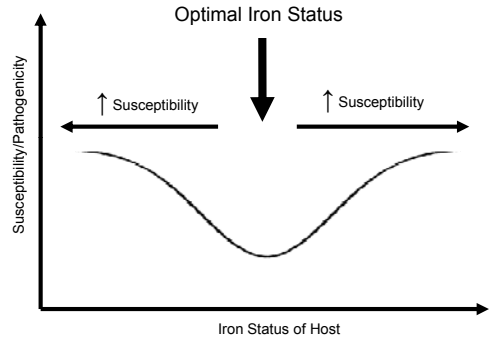
- Productivity expressed as % of average at different weeks during supplementation
- The cost of multi- supplementation per production line of 70 women is about $4 US
- The value of production increase is about $700 US
- Supplementation with iron would be cheaper than $1 US

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%

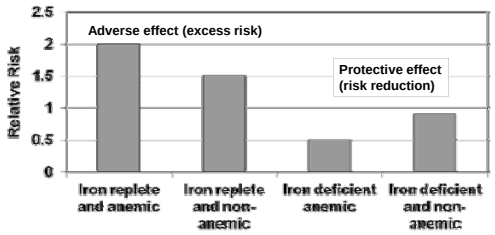
From S. Horton, "The Economics of Nutritional Interventions" In *Nutrition and Health in Developing Countries*.

Iron and Infection



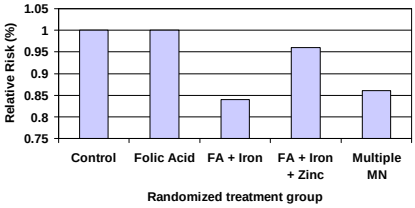
Relative risk of hospitalization associated with daily iron supplementation, by iron status category* at baseline

Zanzibar children, 1-35 mo, 2002-03



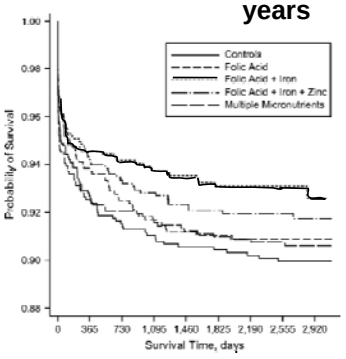
*Iron deficient defined as ZPP > 80 µmol/mol heme; Anemic defined as Hb < 10 g/dL (Sazawal et al., 2008)

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



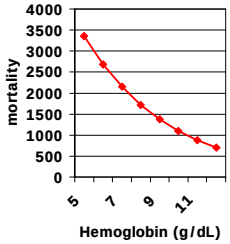
Hazard ratio: 0.58 (0.3

P Christian et al., American Journal of Epidemiology 2009 170(9):1127-1136; doi:10.1093/aje/kwp

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.

At 6.0 g/dL, evidence of circulatory decompensation becomes apparent. Women experience breathlessness and increased cardiac output at rest. At this stage, added stress from labor. . . can result in maternal death. Without effective treatment, maternal death from anemic heart failure . . . is likely with a hemoglobin concentration of 4.0 g/dL. Even a blood loss of 100 mL can cause circulatory shock and death.



Stoltzfus, Mullany & Black, 2003

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)
- Delayed cord clamping at delivery

From: Prentice AM, Prentice A. New Scientist 1988;118[1608]:42.

How can iron supplements reach pregnant women?

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 much time do health services spend on ANC? A recent study in Tanzania

BMC Pregnancy and Childbirth 2006, 6:22 http://www.biomedcentral.com/1471-2393/6/22

Von Both C. et al.

Table 5: Comparison of current performance and anticipated standard of focused ANC model

Activity	Current practise	Focused ANC	Current practise	Focused ANC
	first visit		revisit	
Registration	02:10	05:00	01:30	00:00
History taking	04:20	10:00	01:20	05:00
Examination	03:40	08:00	03:00	08:00
Drug administration	01:00	03:00	01:40	03:00
Immunization	01:40	01:00	01:00	01:00
Health education and counselling	01:30	15:00	00:00	15:00
Total time direct activities	*12:20*	*42:00*	*06:30*	*32:00*
Welcoming the client	01:00	01:00	01:00	01:00
Documentation of findings	02:00	03:00	01:30	03:00
Total contact time	15:20	46:00	09:00	36:00

1 min 30 seconds for counseling

15 min needed

0 time for counseling!

How much time do health services spend on ANC? A recent study in Tanzania

BMC Pregnancy and Childbirth 2006, 6:22 http://www.biomedcentral.com/1471-2393/6/22

Von Both C. et al.

Table 5: Comparison of current performance and anticipated standard of focused ANC model

Activity	Current practise	Focused ANC	Current practise	Focused ANC
	first visit		revisit	
Registration	02:10	05:00	01:30	00:00
History taking	04:20	10:00	01:20	05:00
Examination	03:40	08:00	03:00	08:00
Drug administration	01:00	03:00	01:40	03:00
Immunization	01:40	01:00	01:00	01:00
Health education and counselling	01:30	15:00	00:00	15:00
Total time direct activities	*12:20*	*42:00*	*06:30*	*32:00*
Welcoming the client	01:00	01:00	01:00	01:00
Documentation of findings	02:00	03:00	01:30	03:00
Total contact time	15:20	46:00	09:00	36:00

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

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

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

Processed Fortified Cereal Blends

Lipid-based nutrient supplements

Point-of-use Micronutrient powders

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

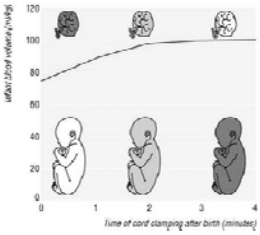
Iron supplements to women and fortification strategies

3 strategies:

- Adequate maternal iron status
- Prevent low birth weight
- Delay cord clamping

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