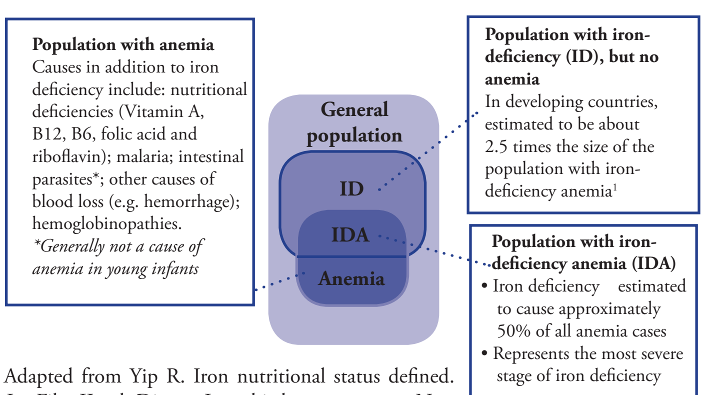
Pan American Health Organization
Regional Office of the World Health Organization

Ensuring a healthy start for future development: Iron nutrition during the first 6 months of life

The importance of iron for healthy development

Iron is an essential nutrient for optimal mental, motor and behavioral development. It is present in all body cells and is fundamental for basic physiological processes such as hemoglobin production and enzyme function. Iron deficiency (ID) generally results when dietary iron intake cannot meet required needs and iron reserves become depleted. Because iron needs are highest during periods of rapid growth or when frequent blood loss occurs (e.g. through menstruation or intestinal bleeding), infants and children, pregnant women and women of reproductive age are at high risk of developing ID.

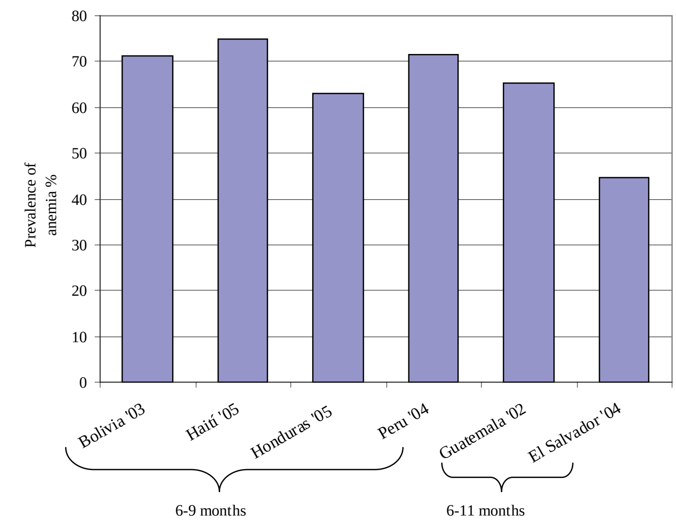
Like other micronutrient deficiencies, ID is generally not outwardly apparent, even though it may already be negatively affecting fundamental physiological processes. In its most advanced stage, when iron stores have been depleted, anemia develops. Anemia is defined as insufficient hemoglobin or red blood cells. Anemia caused by ID is referred to as iron deficiency anemia (IDA). Although ID is thought to be the primary cause of anemia, anemia can have other causes. These include other nutritional deficiencies such as vitamins B12, B6 and A, riboflavin, and folic acid; chronic disease and inflammation; conditions that cause blood loss or hemolysis (e.g. parasitic infections such as hookworm or malaria, or blood loss caused by hemorrhage); and hemoglobinopathies. The relationship between ID, anemia and IDA in the general population is illustrated below.



Adapted from Yip R. Iron nutritional status defined. In: Filer IJ, ed. Dietary Iron: birth to two years. New York, Raven Press, 1989:19-36.

The magnitude of iron deficiency

Figure 1: Prevalence of anemia (hemoglobin < 11 g/dL) among 6 to 11 month-old children in countries in Latin America and the Caribbean



Source: ORC Macro, 2007. MEASURE DHS STATcompiler, http://www.measuredhs.com, September 19 2007; Encuesta Nacional de Salud Familiar, El Salvador 2004; Encuesta Nacional de Salud Materno Infantil, Guatemala, 2002.

The World Health Organization identifies ID as the most common nutritional deficiency in the world, potentially affecting up to 5 billion people.[1] The prevalence of ID has been traditionally estimated from the prevalence of anemia, assuming that approximately half of all anemia cases are caused by ID.[2] However, because anemia can be caused by many factors, this may overestimate the true prevalence of IDA.[3] Nevertheless, the very high prevalence of anemia found in infants and young children throughout most of the developing world indicates that ID is a serious, widespread and persistent public health problem.* The very high prevalence of anemia by 6 months of age among infants in Latin America and the Caribbean (**Figure 1**) as well as in other world regions, is particularly important because it indicates that infants are becoming anemic early in life when iron reserves should still be adequate to meet iron needs. This implies that even greater numbers of infants are likely to be iron-deficient (but not yet anemic) by these ages.

* Appropriate cutoffs for the diagnosis of IDA in infants are still controversial. Alternative cutoffs to the WHO recommended cutoffs have been proposed.[4]

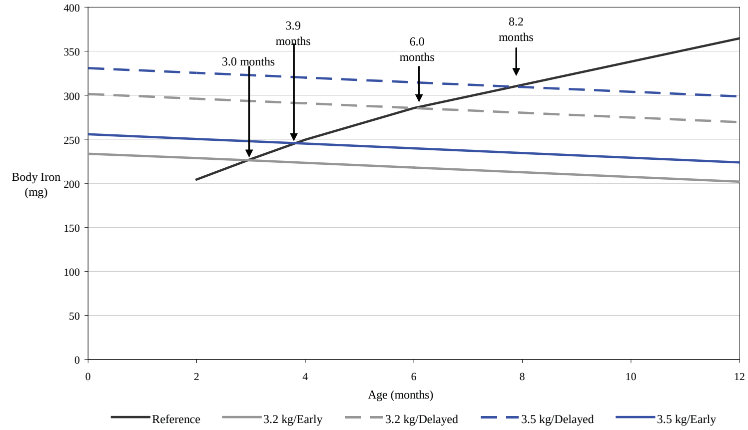
Principal causes of iron deficiency anemia in early infancy

Under normal circumstances, infants should have sufficient iron stores at birth to last for approximately the first 6 to 8 months of life.[5] (**Figure 2**) However, several conditions prevent many infants from reaching this goal:

1) **Inadequate iron status of mothers during pregnancy**
   Ensuring adequate maternal iron status during pregnancy (and before) will also ensure adequate infant iron reserves at birth, as the newborn's iron reserves are dependent on the mother's.[6]
2) **Prematurity (< 37 weeks gestation) and low birth weight (< 2500 grams)**
   The size of birth iron stores (in liver and other tissues) is positively related to birth weight, and the last 8 weeks of gestation are particularly important for the increase in total iron in these storage organs. Thus smaller infants and those born prematurely will have smaller iron reserves at birth and are at greater risk of developing iron deficiency early in life.
3) **Inappropriate clamping of the umbilical cord (i.e. immediately or before cord pulsations cease) after delivery**
   Clamping the umbilical cord immediately after birth will prevent the infant from receiving adequate blood from the placenta and thus the full endowment of total body iron at birth. Between 30-50% of newborn blood volume is provided through delayed cord clamping (i.e. at the end of cord pulsations, approximately 2-3 minutes after delivery).[5] Thus immediate clamping, by preventing a significant transfer of placental blood to the infant, will also reduce the size of total body iron at birth.

In many countries in the Latin American and Caribbean region, as well as other world regions, maternal iron deficiency is prevalent, low birth weight and preterm deliveries are common, and immediate umbilical cord clamping is frequently practiced. In addition, introduction of non-breastmilk liquids and solids before 6 months of age is common, which also can contribute to poor iron status.

Figure 2: How long should birth iron stores last? An analysis by birth weight and cord clamping time.



The black line indicates the estimated body iron needed to maintain adequate hemoglobin levels and provide for growth (i.e. the "reference" body iron needed). The blue and gray lines indicate the levels of body iron available for the first 12 months of life (including the birth iron stores and iron provided through breast milk) for 4 different scenarios of birth weight and cord clamping time.[5] The intersection of each blue/gray line with the black line indicates the point at which body iron becomes insufficient to support growth and haemoglobin concentrations.

Importance of preventing iron deficiency anemia in infancy

In infants and children, ID and IDA are of particular concern because of their negative and perhaps irreversible effects on cognitive, motor and behavioral development. Long-term studies indicate the importance of their prevention, since treatment to correct these conditions may not reverse their negative effects (see Box). Infants and young children with anemia are likely to have delayed psychomotor development when they reach school age, contributing to impaired performance on motor and cognitive development tests, equivalent to a 1-2 point deficit in IQ.[7]

Prevention is doubly important because iron excess also has negative consequences. Iron supplements, when given to infants who already have adequate iron stores or who live in regions where malaria is endemic, can have negative effects on growth,[8] and increase morbidity and mortality.[8,9] Thus public health interventions to avoid the negative effects of ID and IDA need to focus on preventing their development. Improving iron status at birth and promoting appropriate infant feeding practices during the first 6 months of life will help to prevent ID and IDA during this period, before other appropriate feeding practices can be promoted.

Long-lasting negative effects of iron deficiency anemia on neurodevelopment

Iron deficiency anemia occurring during infancy (between 6 to 24 months of age) is associated with poorer cognitive, motor, and/or social/emotional outcomes as compared to outcomes in infants that did not suffer from iron deficiency anemia.[20] Of even more concern are the results of studies that show remaining developmental deficiencies in anemic or chronically iron deficient infants who received treatment to correct the deficiency and/or anemia. One study of 6-month old infants showed slower conduction times for auditory brainstem responses in infants with iron deficiency anemia, as compared to normal controls, suggesting that nerve myelination may have been altered in the infants suffering from iron deficiency anemia.[21] Of particular concern was that 4 years later, following treatment to correct the anemia, the originally anemic infants still showed poorer outcomes than the control infants.[22] Similarly, a recent follow-up study of a cohort of Costa Rican adolescents that had been tested for iron deficiency anemia as infants and children, showed that at 19 years of age, middle-socioeconomic status participants who had chronic iron deficiency as infancy and received treatment scored on average 9 points lower on cognitive testing than their peers of similar socioeconomic status who had not suffered from iron deficiency anemia.[23] For low socioeconomic status young adults, the difference in cognitive test scores associated with iron deficiency anemia during infancy was nearly tripled to 25 points, indicating the compounded negative effect of lower-socioeconomic status and iron deficiency on cognitive development.

Ensuring and protecting adequate iron status in early infancy

OPTIMIZING BIRTH TOTAL BODY IRON

Total body iron at birth is one of the most important factors for maintaining adequate iron status during the first half of infancy.[10,11] Preventative actions to optimize birth total body iron include:

1) **Ensuring adequate maternal iron status during pregnancy, and ideally, before conception**

   To ensure adequate iron status of women during pregnancy, it is essential to improve the iron status of women before they conceive. This includes improving nutritional status in adolescents particularly, as the nutritional demands of pregnancy will be combined with their own nutritional needs for their continued growth. Actions to improve iron status among women of reproductive age before and during pregnancy include:

   - Encouraging consumption of iron-rich (e.g. a source of heme-iron, such as that found in red meat) and iron-fortified foods. Consumption of heme iron, in particular, also improves the absorption of the non-heme forms of iron found in plants. Reducing intake of foods high in phytates such as coffee, tea, legumes and whole cereals at mealtime will also improve iron absorption.
   - Treating intestinal parasites in the second trimester in areas where hookworm is endemic (20-30% prevalence). In areas where hookworm infection prevalence exceeds 50% antihelminthic treatment should be repeated in the third trimester.[13]
   - Supplementing pregnant women with iron will allow them to meet their iron requirements. Recommendations for pregnant women and adolescent females are included in Table 1.

2) **Decreasing the prevalence of low birth weight and preterm births**

   Actions to decrease the risk of low-birth-weight and preterm births include:

   - Reducing adolescent pregnancies.
   - Improving maternal nutritional status before pregnancy (including adequate energy, protein, and micronutrient intake) to ensure appropriate pre-pregnancy weight (with respect to both underweight and obesity) and nutrient reserves.
   - Spacing pregnancies at least 2 years apart.[12]
   - Ensuring adequate maternal weight gain during pregnancy.
   - Eliminating smoking during pregnancy.
   - Preventing and treating maternal malaria. Women in their first or second pregnancies with malaria should be treated with curative anti-malarials at the first prenatal visit followed by antimalarial prophylaxis.[13]
   - Preventing and treating reproductive tract infections (e.g. bacterial vaginosis).

3) **Practicing delayed umbilical cord clamping at delivery to ensure that the newborn begins life with adequate total body iron**

   Waiting just 2-3 minutes (i.e. at the end of cord pulsations) to clamp the umbilical cord at birth provides the newborn with adequate blood volume and the full endowment of total body iron, which is essential for preventing the development of iron deficiency during

Table 1: Guidelines for iron supplementation of pregnant women and infants to prevent iron deficiency anemia by group and population prevalence of anemia

Group	If population prevalence of anemia is...	Recommended dose	Duration
Pregnant women	< 40%	60 mg iron + 400 µg folic acid daily	6 months in pregnancy
	≥ 40%	60 mg iron + 400 µg folic acid daily	6 months in pregnancy continuing for 3 months postpartum
Adolescent females	—	60 mg iron + 400 µg folic acid*	—
Low-birth weight infants	—	12.5 mg iron + 50 µg folic acid daily	2-24 months of age

*Dosing regimen currently undefined.
Sources: Stoltzfus RJ, Dreyfuss ML. Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia. Washington D.C.: International Life Sciences Institute Press, 1998; and Iron and folate supplementation. Standards for Maternal and Neonatal Care. Department of Making Pregnancy Safer, WHO Geneva, 2006.

the first 6 months of life. The difference in body iron stores at 6 months of age between early and delayed clamped infants is equivalent to 1-2 months of iron requirements.[14] Delayed cord clamping will benefit all infants, including term and preterm infants, and will be particularly important for those infants who may already have compromised iron reserves because of smaller birth size or maternal ID.[14]

OPTIMIZING INFANT FEEDING PRACTICES: EXCLUSIVE BREASTFEEDING FOR THE FIRST 6 MONTHS OF LIFE TO PROTECT INFANT IRON STATUS

Because of its enormous benefits to infant nutrition and prevention of infant morbidity and mortality, exclusive breastfeeding (breastmilk as the sole source of food, with no other liquids or solids used, except for medicines, or vitamin/mineral drops or syrups) is recommended for the first 6 months of life. Although breastmilk is not high in iron, its iron is relatively well-absorbed, (range from 12-56%)[5], particularly for infants with lower iron levels.[15] Introducing other liquids or solids during the first 6 months of life can have negative effects on infant iron status; these foods (except for iron-fortified formula) are generally low in iron which is poorly absorbed, and can also interfere with the absorption of breastmilk iron.[16,17] In low birth weight infants, even introducing iron-fortified solids before 6 months of age can interfere with the absorption of iron from supplements, which are recommended for this group of infants.[18] Early use of cow's milk can also be a contributor to iron loss by causing small blood loss in the intestine.[19] Preventative actions to protect infant iron status include:

1) **Supporting and encouraging initiation of exclusive breastfeeding within one hour of birth**
   Early initiation of breastfeeding prevents neonatal illness and death and will improve long-term breastfeeding practices. Hospital practices and environments that are known to promote early initiation and establishment of breastfeeding include:
   - Immediate skin-to-skin contact between mother and infant.
   - Putting the infant to the breast within the first hour of life.
   - Delaying routine newborn procedures for at least 1 hour after birth.
   - Rooming-in to encourage breastfeeding on demand
   - Avoidance of non-breastmilk fluids, pacifiers or artificial nipples.
2) **Avoiding introduction of non-breastmilk liquids (including water) or solids before 6 months of age**
   Introducing other foods or liquids before 6 months of age has negative effects for the infant and mother.
   For the mother, providing foods and liquids other than breastmilk to the infant leads to:
   - Decreased breastmilk production which shortens the duration of breastfeeding.
   - Decreased length of lactational amenorrhea, which will negatively affect maternal iron status because of the return of menstruation, and can also decrease

birth spacing intervals in the absence of contraception further compromising maternal iron stores.

For the infant, receiving foods and liquids other than breast milk can lead to:

- Decreased nutritional status because of the low nutrient content and bioavailability of liquids and foods commonly fed to infants.
- Increased risk of illness and death from infection. Providing other non-breast milk (and thus, non-sterile) liquids and foods not only provides an easy route of entry for viruses and bacteria, but also compromises the barrier function of the intestinal lining, which serves as a primary line of defense against pathogens.

Special considerations for low birth weight infants

Because of their smaller iron stores at birth, low birth weight infants will need an additional source of iron before 6 months of age. Iron supplements starting at 2 months of age are recommended for infants weighing less than 2500 grams at birth (**Table 1**).

Remaining challenges

Assessing iron status and anemia in this population is challenging, especially in low-resource environments where universal screening of infants for IDA at early ages is not feasible for logistical, cost, and frequently, cultural reasons. However, many infants will have become iron deficient and anemic before 6 months of age because the previous actions discussed have not been met, and thus may need iron supplements before this time. At the same time, universal supplementation of infants before 6 months of age may have negative consequences in infants whose iron reserves are already adequate. Thus, ideally, feasible and affordable screening measures that rely on alternative methods of identifying infants at high risk of developing IDA before 6 months of age are needed (i.e. developing easy to-use, rapid tests for measuring irons status, similar to the HemoCue for hemoglobin; or creating screening tools that do not require blood to be taken).

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Acknowledgements

This informational bulletin was written in 2008, by Camila M. Chaparro and Chessa K. Lutter. We would like to thank and acknowledge the following individuals for their valuable comments: Andre Briend (World Health Organization), Esther Casanueva (National Institute of Perinatology, Mexico), Kathryn G. Dewey (University of California at Davis), Juan-Pablo Pena Rosa (World Health Organization) and Kelley Scanlon (US Centers for Disease Control and Prevention).

For more information, please contact

Newborn, Child and Youth Health
Family Community Health
Pan American Health Organization
525 23rd Street, NW, Washington D.C. 20037
Tel.: 202 974-3519
Website: www.paho.org

Pan American Health Organization
Regional Office of the World Health Organization