# IRON DEFICIENCY ANEMIA

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Iron deficiency is the most prevalent nutritional deficiency and the most common cause of anemia in the United States.[1] Iron deficiency anemia is characterized by a defect in hemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic).[2] The capacity of the blood to deliver oxygen to body cells and tissues is thus reduced.

According to the third National Health and Nutrition Examination Survey (NHANES III) data, iron deficiency, defined by two or more abnormal measurements (serum ferritin, transferrin saturation and/or erythrocyte protoporphyrin), continues to be relatively prevalent in U.S. females, affecting 7.8 million adolescents and women of childbearing age.[3] Iron deficiency anemia, a more severe stage of iron deficiency (defined as a low hemoglobin in combination with iron deficiency), was found in 3.3 million females.[3] The prevalence of iron deficiency and anemia in adolescent males and females, based on the 5th percentile, NHANES III data, is listed in Table 1.

**TABLE 1**
**Prevalence of Iron Deficiency and Iron Deficiency Anemia in Adolescent Males and Nonpregnant Females**

| Gender/Age (yrs) | Iron Deficiency | Iron Deficiency Anemia |
|---|---|---|
| **Females** | | |
| 12-15 | 9% | 2% |
| 16-19 | 11% | 3% |
| **Males** | | |
| 12-15 | 1% | <1% |
| 16-19 | <1% | <1% |

Source: Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency anemia in the United States. Morb Mortal Wkly Rep 1998; 47:1-29.

A two to three times higher prevalence of iron deficiency was found in Mexican-American, compared to white, non-Hispanic adolescent females.[4] Higher rates were also noted in other minority and low income populations.[3]

## SIGNIFICANCE

Iron is essential to all cells. Functions of iron include involvement in energy metabolism, gene regulation, cell growth and differentiation, oxygen binding and transport, muscle oxygen use and storage, enzyme reactions, neurotransmitter synthesis, and protein synthesis.[1,2,5] Potential

consequences of iron deficiency, which occur in relation to its severity, are summarized in Table 2, while symptoms associated with anemia are listed in Table 3.

**TABLE 2**
**Potential Consequences of Iron Deficiency**

| | |
|---|---|
| Decreased maximum aerobic capacity | Impaired cognitive functioning and memory |
| Decreased athletic performance | Decreased school performance |
| Lowered endurance | Compromised growth and development |
| Decreased work capacity | Increased lead and cadmium absorption |
| Impaired temperature regulation | Increased risk of pregnancy complications, including prematurity and fetal growth retardation |
| Depressed immune function | |
| Increased rates of infection | |

Sources: Compiled from Provan D. Mechanisms and management of iron deficiency anaemia. Br J Haematol 1999; 105 Suppl 1:19-26; Frith -Terhune AL, Cogswell ME, Khan LK, Will JC, Ramakrishnan U. Iron deficiency anemia: higher prevalence in Mexican American than in non-Hispanic white females in the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 2000; 72:963-968; Beard J, Tobin B. Iron status and exercise. Am J Clin Nutr 2000;72(2 Suppl):594S-697S.

**TABLE 3**
**Symptoms Associated With Iron Deficiency Anemia**

| | |
|---|---|
| Fatigue | Pallor |
| Lethargy | Flattened, brittle nails (spoon nail) |
| Dizziness | Angular stomatitis (cracks at mouth corners) |
| Headaches | Glossitis |
| Shortness of breath | Blue sclera (whites of eyes) |
| Ringing in ears | Pale conjunctivae |
| Taste disturbances | Pica (ice chewing) |
| Restless leg syndrome | |

Sources: Compiled from Provan D. Mechanisms and management of iron deficiency anaemia. Br J Haematol 1999; 105 Suppl 1:19-26; Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001; 131:568S-580S; Frewin R, Hensen A, Provan D. ABC of clinical haematology: iron deficiency anaemia. Br Med J 1997; 314:360-363.

## ETIOLOGY

Adolescents are vulnerable to iron deficiency because of increased iron requirements related to rapid growth. Iron needs are highest in males during peak pubertal development because of a greater increase in blood volume, muscle mass and myoglobin.[1,6] After menarche, iron needs continue to remain high in females because of menstrual blood loss, which averages about 20 mg of iron per month, but may be as high as 58 mg in some individuals.[5] Oral contraceptives decrease menstrual losses, while some intrauterine devices may increase losses.

In spite of increased iron needs, many adolescents, particularly females, may have iron intakes of only 10-11 mg/day of total iron, resulting in approximately 1 mg of absorbed iron.[5] About three-fourths of adolescent females do not meet dietary iron requirements, compared to 17% of males.[1] Conditions which increase the risk for iron deficiency in adolescents are summarized in Table 4.

**TABLE 4**
**Risk Factors for Iron Deficiency**

| **Inadequate iron intake/absorption/stores** | **Increased iron requirements/losses** |
|---|---|
| Vegetarian eating styles, especially vegan diets | Heavy/lengthy menstrual periods |
| Macrobiotic diet | Rapid growth |
| Low intakes of meat, fish, poultry or iron fortified foods | Pregnancy (recent or current) |
| Low intake of foods rich in ascorbic acid | Inflammatory bowel disease |
| Frequent dieting or restricted eating | Chronic use of aspirin or nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) or corticosteroid use |
| Chronic or significant weight loss | Participation in endurance sports (e.g., long distance running, swimming, cycling) |
| Meal skipping | Intensive physical training |
| Substance abuse | Frequent blood donations |
| History of iron deficiency anemia | Parasitic infection |
| Recent immigrant from developing country | |
| Special health care needs | |

Sources: Compiled from Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency anemia in the United States. Morb Mortal Wkly Rep 1998; 47:1-29; Provan D. Mechanisms and management of iron deficiency anaemia. Br J Haematol 1999; 105 Suppl 1:19-26; Frewin R, Hensen A, Provan D. ABC of clinical haematology: iron deficiency anaemia. Br Med J 1997; 314:360-363; Wharton B. Iron deficiency in children: detection and prevention. Br J Haematol 1999; 106:270-280.

## SCREENING/DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) recommendations for screening adolescents for anemia suggest that all females be screened at least once every five years unless risk factors for anemia are present, resulting in the need for annual anemia screening.[1] Adolescent males only need to be screened for anemia in the presence of risk factors.

When iron status is adequate, iron stores and erythropoiesis remain normal. With iron depletion, stores are reduced while erythropoiesis is maintained. Iron deficiency is associated with depleted stores and abnormalities in iron metabolism and red blood cell biochemistry. Although there is no single laboratory test that specifically indicates iron deficiency anemia, several tests are used to determine iron status and the presence of anemia (see Table 5).

**TABLE 5**
**Hemoglobin and Hematocrit Values Diagnostic of Anemia**

| Gender/Age (yrs) | Hemoglobin<g/dL | Hematocrit<% |
|---|---|---|
| Females | | |
| 12-14.9 | 11.8 | 35.7 |
| 15-17.9 | 12.0 | 35.9 |
| 18+ | 12.0 | 35.9 |
| Males | | |
| 12-14.9 | 12.5 | 37.3 |
| 15-17.9 | 13.3 | 39.7 |
| 18+ | 13.5 | 39.9 |

| Laboratory Test | Value |
|---|---|
| Ferritin | <15 ug/L |
| Serum transferrin receptor concentration (TfR) | >8.5 mg/L |
| Transferrin saturation | <16% |
| Mean cell volume (MCV) | <82/85 fL* |
| Red cell distribution width (RDW) | >14% |
| Erythrocyte protoporphyrin (FEP) | >70 ug/dL |

* <15 yrs/>15 yrs of age

Source: Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency anemia in the United States. Morb Mortal Wkly Rep 1998; 47:1-29.

## Hemoglobin/Hematocrit

Measurement of hemoglobin or hematocrit is the most cost efficient and commonly used method to screen for anemia. Determining the concentration of hemoglobin, an iron-containing protein, in red blood cells is a more sensitive and direct indicator of anemia than hematocrit (percentage of red blood cells in whole blood).[1] Values obtained from capillary (fingerstick) blood are less reliable than those from venous blood since variation in technique can alter results. Low capillary values should thus be confirmed using blood obtained from venipuncture.

Altitudes above 3000 feet raise the cutpoint for anemia because of lower oxygen partial pressure, a reduction in oxygen saturation of blood, and an increase in red blood cell production. Cigarette smoking also raises the cutpoint for anemia because carboxyhemoglobin formed from carbon monoxide during smoking has no oxygen-carrying capacity.[1]

Adjustment of hemoglobin and hematocrit values for the effects of altitude and/or smoking in the diagnosis of anemia is summarized in Table 6.

**TABLE 6**
**Adjustment of Hemoglobin and Hematocrit Values for the Diagnosis of Anemia**

| Altitude (feet) | Hemoglobin g/dL | Hematocrit % |
|---|---|---|
| 3,000-3,999 | +0.2 | +0.5 |
| 4,000-4,999 | +0.3 | +1.0 |
| 5,000-5,999 | +0.5 | +1.5 |
| 6,000-6,999 | +0.7 | +2.0 |
| 7,000-7,999 | +1.0 | +3.0 |
| **Cigarettes/Day** | | |
| 10-19 | +0.3 | +1.0 |
| 20-39 | +0.5 | +1.5 |
| 40+ | +0.7 | +2.0 |

Source: Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency anemia in the United States. Morb Mortal Wkly Rep 1998; 47:1-29.

With a low hemoglobin/hematocrit, a presumptive diagnosis of iron deficiency anemia is supported by a response to iron therapy. If the adolescent's hemoglobin does not improve after taking iron supplements for one month, further assessment is indicated. [1]

- A low serum ferritin (<15 ug/L), in addition to a low hemoglobin or hematocrit, confirms the diagnosis of iron deficiency anemia.[1]
  - An intracellular iron storage protein, serum ferritin reflects iron reserves (1 ug/L=8-10 mg stored iron).[2]
  - Since the normal range of hemoglobin in African Americans is approximately 0.8 g/dL lower than whites, a serum ferritin level can also be useful in identifying iron deficiency in those with mild anemia.[1]
  - A ferritin level at or above 15 ug/L is suggestive of anemia not related to iron deficiency. However, since ferritin is an acute phase protein, ferritin levels may be normal or elevated when iron deficiency and infection, chronic inflammation, malignancy or conditions causing organ or tissue damage (e.g., arthritis, hepatitis) occur simultaneously.[2]
- An elevated serum transferrin receptor concentration (TfR) (>8.5 mg/L) is an early and sensitive indicator of iron deficiency. It is, however, also raised in Thalassemia and hemolytic anemias.[2]
  - Serum transferrin, an iron transport protein, increases when iron stores are low. TfR reflects the number of transferrin receptors on immature red cells, and thus tissue iron need.[6]
  - Serum TfR concentration remains normal when chronic disease, inflammation or infection are present, distinguishing iron deficiency anemia from anemia of chronic disease.[7]
  - If iron deficiency anemia and anemia associated with chronic disease occur simultaneously, TfR concentration is elevated.

### Additional Screening

In adolescents who have iron deficiency which is not responsive to iron therapy, additional screening may be indicated to rule out the following:[1]

- Sickle cell trait and Thalassemia in adolescents who are African American, African, Southeast Asian or of Mediterranean descent.
- Parasitic infections (e.g., in newly arrived immigrants or travelers from developing countries).
- Anemia related to folate or vitamin $B_{12}$ deficiency or infection or chronic inflammation.

## INTERVENTION

Iron therapy, in combination with dietary strategies to increase iron and vitamin C intakes, effectively treats iron deficiency anemia by raising the hemoglobin level and replacing iron stores. The CDC recommends an iron dosage of 60 mg of elemental iron, 1-2 times per day, for adolescents with anemia.[1] Examples of iron supplements and their elemental iron content are included in Table 7. Ferrous sulfate is the least expensive and most commonly used iron preparation.

**TABLE 7**
**Examples of Iron Supplements**

| Supplement | Total Iron (mg) | Elemental Iron (mg) |
|---|---|---|
| Ferrous sulfate | 324 | 66 |
| Ferrous gluconate | 325 | 36 |
| Feostat chewable | 100 | 33 |
| Feostat liquid | 100 | 33/5 mL |
| Slow Fe | 160 | 50 |
| Fe 50 extended release | 160 | 50 |
| Ferro-Sequels timed release | 50 | 50 |
| Feosol caplets | 50 | 50 |

Source: Drug facts and comparisons. St. Louis, MO: Facts and Comparisons, 1998.

Iron is absorbed primarily in the duodenum and upper jejunum, where the acidic environment keeps iron in its soluble form. Beyond these sites, bicarbonate makes iron less soluble.[2] Delayed release iron preparations, although better tolerated, may be less effective and are expensive.

A multivitamin containing copper and zinc will prevent impaired absorption or utilization of these nutrients when therapeutic dosages of iron are used. Since the calcium, phosphorous and magnesium contained in multivitamins can impair iron absorption, the iron content of these supplements should not be included in the therapeutic iron dose. For the same reason, the iron supplements and multivitamin should be taken at separate times.

Iron supplements are absorbed most effectively when taken on an empty stomach. If gastrointestinal intolerance occurs (nausea, constipation, diarrhea, abdominal pain or cramping), taking the supplements with food or at bedtime may alleviate these symptoms. Side effects can also

be minimized by increasing the dosage gradually, using a lower dosage of iron, or using a preparation with a lower elemental iron content, such as ferrous gluconate. Taking iron supplements on a less than daily basis may not only improve tolerance, but may be as effective, since saturation of the red cells with iron reduces further absorption for a few days.[6]

The extent of iron absorption is determined not only by the body's need for iron, but the absence of inhibiting factors. To maximize absorption, iron supplements should be taken with liquids other than milk, coffee, tea or phosphate-containing carbonated beverages such as soft drinks.[8] In addition, they should not be taken within one hour of tetracylines, antacids, acid blockers, calcium supplements or multivitamins.[7] Iron deficiency anemia is usually resolved after six to eight weeks of treatment. Inadequate response may be related to continued blood loss (e.g., heavy menses or analgesic use), inflammation, ineffective absorption, or poor compliance.[1] After the hemoglobin has returned to normal, continuing to take a low dosage of iron (e.g., 30 mg/day) for an additional one to two months will replace iron stores and decrease the likelihood of reoccurrence of anemia.

### Dietary Strategies

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 (see Table 8).[2]

**TABLE 8**
**Dietary Factors That Enhance and Inhibit Iron Absorption**

| Enhance | Inhibit |
|---|---|
| Meat | Phosphate |
| Fish | Calcium |
| Poultry | Tea (tannic acid) |
| Seafood | Coffee |
| Gastric acid | Colas |
| Ascorbic acid | Soy protein |
| Malic acid | High doses of minerals |
| Citric acid | Bran/fiber |

Source: Compiled from Provan D. Mechanisms and management of iron deficiency anaemia. Br J Haematol 1999; 105 Suppl 1:19-26; Wharton B. Iron deficiency in children: detection and prevention. Br J Haematol 1999; 106:270-280; Cook JD. The measurement of serum transferring receptor. Am J Med Sci 1999;318:269-276.

## COUNSELING

To increase compliance with iron therapy, inform the adolescent of its importance, the possibility of side effects (which will subside with continued use) and that iron supplements may darken stools. Help the adolescent remember to take the supplement by suggesting keeping some in a locker, purse, car or with the school nurse. The adolescent could also put up signs or set a beeper or watch as a reminder.

To protect their potency, recommend that iron supplements be stored away from heat and humidity (e.g., not in bathroom). To prevent accidental poisoning, caution the adolescent to keep the supplement in its protective packaging, away from children and pets.

Encourage frequent consumption of meat, fish, poultry and consumption of vitamin C sources with meals to enhance iron absorption. Suggest iron-rich snacks, such as fortified breakfast cereals, grain products, meat sandwiches, bean burritos, fajitas, hamburgers, Chex® mix, dried fruits, nuts, soy nuts, molasses cookies, and edamame (green soy beans in pods). Discourage meal skipping and dieting. Suggest limiting coffee, tea, iced tea, carbonated beverages, low nutrient snacks, and excessive milk consumption (more than 4 cups per day).

## REFERRAL

Adolescents with severe or prolonged iron-deficiency anemia may benefit from referral to a registered dietitian or nutritionist for more intensive nutrition assessment and counseling. Collaboration with a school or public health nurse may also be helpful in cases of iron-deficiency anemia that do not respond to therapy.

## PREVENTION

- Encourage adolescents, particularly those with risk factors for iron-deficiency anemia, to follow the dietary strategies discussed above.
- Adolescents who are at high risk for anemia, such as female athletes with heavy menses, may benefit from routine or periodic use of a low dose iron supplement.

## REFERENCES

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