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Anemia

Highlights

Erythropoiesis-Stimulating Drugs

In 2006, the Food and Drug Administration (FDA) issued an advisory regarding treatment targets for erythropoiesis-stimulating drugs. These drugs include epoetin alfa (Procrit, Epogen, and Eprex) and darbepoetin alfa (Aranesp). They are used to treat severe anemia caused by other diseases, such as chronic kidney disease.

Two 2006 studies in the *New England Journal of Medicine* indicated that aggressive dosing to completely normalize anemia (hemoglobin levels of 13.5 g/dL) provided no greater benefit than lower dosing to partially correct anemia (hemoglobin levels of 10 – 12 g/dL). Higher dosing and higher hemoglobin levels increased the risk for heart failure, heart attack, and stroke.

In response to these studies, the FDA recommends that patients who take these drugs should:·

- Maintain hemoglobin levels that do not exceed 12 g/dL.
- Receive frequent blood tests to monitor hemoglobin levels.
- Contact their doctors if they experience such symptoms as shortness of breath, pain, swelling in the legs, or increases in blood pressure.

Anemia in the Elderly

Mild anemia may cause difficulties with problem-solving abilities and other cognitive functions, suggests a 2006 study in the *Journal of the American Geriatrics Society*.

Diagnosing Fetal Anemia

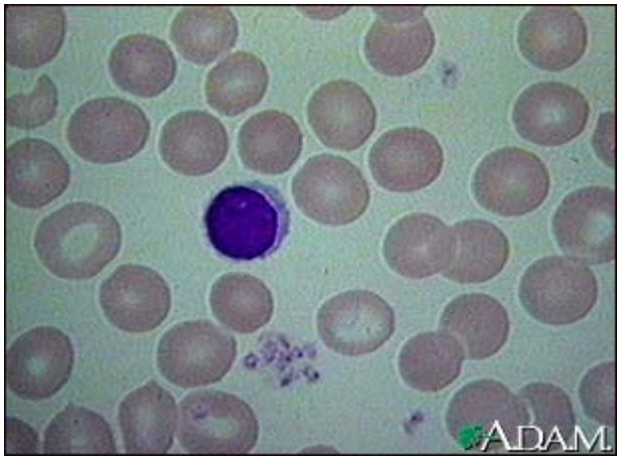
Doppler ultrasonography may be better and safer than amniocentesis for diagnosing fetal anemia, according to a 2006 study in the *New England Journal of Medicine*. Doppler ultrasonography is a non-invasive imaging test.

Investigational Drugs

Eculizumab, an investigational monoclonal antibody drug, may help improve anemia in patients with paroxysmal nocturnal hemoglobinuria (PNH), indicates a 2006 study in the *New England Journal of Medicine*. PNH is a rare and severe form of hemolytic anemia. There are few treatment options for this condition.

Introduction

Anemia is an abnormal reduction in red blood cells.



This photmicrograph shows normal red blood cells (RBCs) as seen in the microscope after staining.

Anemia is a global problem, at its worst in developing countries. But it is by no means absent in industrialized nations. An estimated 3.4 million Americans suffer from anemia. Anemia is not a single disease but a condition, like fever, with many possible causes and many forms. Causes of anemia include nutritional deficiencies, inherited genetic defects, medication-related side effects, and chronic disease. It can also occur because of blood loss from injury or internal bleeding, the destruction of red blood cells, or insufficient red blood cell production. The condition may be temporary or long term, and can manifest in mild or severe forms.

As it is impossible to discuss all types of anemia, this report focuses on three of the most common forms:

- Iron deficiency anemia
- Anemia of chronic disease (ACD)
- Megaloblastic anemia (caused by deficiencies in the B vitamins folate, vitamin B12, or both)

Some less common causes and types of anemia are included in a table in this report.

Blood

Blood has two major components:

- Plasma is a clear yellow liquid that contains proteins, nutrients, hormones, electrolytes, and other substances. It constitutes about 55% of blood.
- White and red blood cells and platelets make up the balance of blood. The white cells are the infection fighters for the body, and platelets are necessary for blood clotting. The important factors in anemia, however, are red blood cells.

Red blood cells (RBCs), also known as *erythrocytes*, carry oxygen throughout the body to nourish tissues and sustain life. Red blood cells are the most abundant cells in our bodies. Men have about 5.2 million red blood cells per cubic millimeter of blood, and women have about 4.7 million per cubic millimeter of blood.

Hemoglobin and Iron

Each red blood cell contains 200 - 300 *hemoglobin* molecules. Hemoglobin is a complex molecule, and it is the most important component of red blood cells. It is composed of protein (*globulin*) and a molecule (*heme*), which binds to iron.

In the lungs, the heme component binds to oxygen in exchange for carbon dioxide. The oxygenated red blood cells are then transported to the body's tissues, where the hemoglobin releases the oxygen in exchange for carbon dioxide, and the cycle repeats. The oxygen is used in the *mitochondria*, the power source within all cells.

Red blood cells typically circulate for about 120 days before they are broken down in the spleen. Most of the iron used in hemoglobin can be recycled from there and reused.

Structure and Shape of Red Blood Cells

Red blood cells -- the erythrocytes -- are extremely small and look something like tiny, flexible inner tubes. This unique shape offers many advantages:

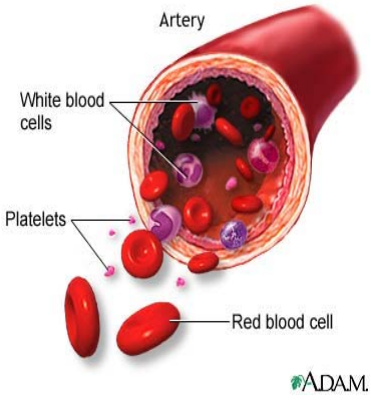
- It provides a large surface area to absorb oxygen and carbon dioxide.
- Its flexibility allows it to squeeze through capillaries, the tiny blood vessels that join the arteries and veins.

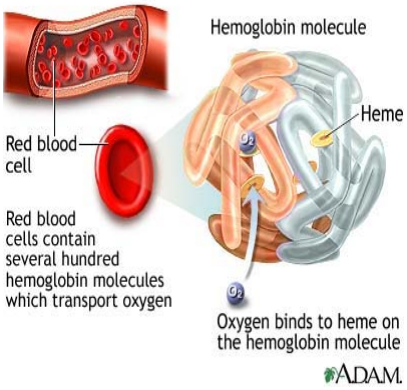
Abnormally shaped or sized erythrocytes are typically destroyed and eliminated.

Blood Cell Production (Erythropoiesis)

The actual process of making red blood cells is called *erythropoiesis.* (In Greek, *erythro* means "red," and *poiesis* means "the making of things.") The process of manufacturing, recycling, and regulating the number of red blood cells is complex and involves many parts of the body:

- The body carefully regulates its production of red blood cells so that enough are manufactured to carry oxygen but not so many that the blood becomes thick or sticky (viscous).
- Most of the work of erythropoiesis occurs in the bone marrow. In children younger than 5 years old, the marrow in all the bones of the body is enlisted for producing red blood cells. As a person ages, red blood cells are eventually produced only in the marrow of the spine, ribs, and pelvis.
- If the body requires an increase in oxygen (at high altitudes, for instance), the kidney triggers the release of the hormone erythropoietin (EPO), a hormone that acts in the bone marrow to increase the production of red blood cells.
- The life span of a red blood cell is between 90 - 120 days. Old red blood cells are removed from the blood by the liver and spleen.
- There they are broken down and iron is returned to the bone marrow to make new cells.





Iron Deficiency Anemia

Iron deficiency anemia occurs when the body lacks mineral iron to produce the hemoglobin it needs to make red blood cells. In general, there are three stages leading from iron deficiency to anemia:

- First, there is an insufficient supply of iron, and iron stores are depleted in the bone marrow. This stage generally has no symptoms.
- Second, iron deficiencies develop and begin to affect hemoglobin production. (Tests, in such cases, reflect low hemoglobin and hematocrit levels.)
- Hemoglobin production declines to the point where anemia develops.

Most of the iron used in the body can be recycled from blood and reused. Nevertheless, iron deficiency can occur from a number of conditions.

Iron-Poor Diets. A healthy diet easily provides enough iron. In general, most people need just 1 mg, and menstruating women need 2 mg of extra iron each day. This means that lack of iron in the diet is not a common cause of iron deficiency anemia, except in infants. In fact, most American adults may be consuming too much iron in their diet. Most of the iron in red blood cells is recycled and reused. Iron-poor diets are a cause of anemia only in people with existing risks for iron deficiency.

Peptic Ulcers and Their Causes. The bacteria *H. pylori* are known to be primary causes of peptic ulcers, and many older people with ulcers have anemia. Anemia in such cases, however, may not result from bleeding ulcers. Instead, anemia is more likely due to the presence of bacteria impairing the ability of these people to absorb iron or vitamin B12. The bacteria, in fact, may also bind to iron and reduce its availability in the intestine, causing iron deficiency anemia.

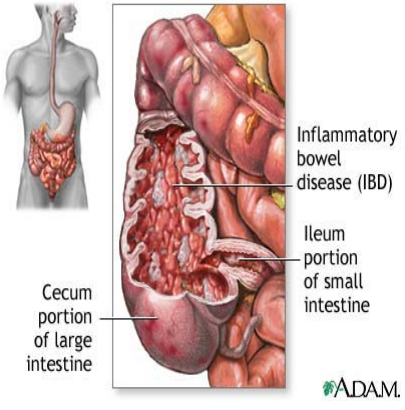
Medications (NSAIDs). Aspirin and drugs such as ibuprofen and naproxen are called nonsteroidal anti-inflammatory drugs (NSAIDs). About 70% of long-term users of these medications have some sign of gastrointestinal bleeding, although it is rarely significant enough to cause anemia.

Bleeding Due to Other Medical Conditions. Iron deficiencies most commonly occur from internal blood loss due to other conditions that range in severity from hemorrhoids toheavy menstruation to benign colon polyps to colon cancer. Very heavy periods (menorrhagia) are the most common causes of anemia in premenopausal women. Cancers of the gastrointestinal tract account for 2% of cases of iron deficiency (the rate is higher when menorrhagia is excluded).

Pica. Pica is the craving for non-food substances such as ice, starch, or clay. It is a possible cause of iron deficiency, particularly in those who eat clay or starch, which interferes with iron absorption in the stomach. To complicate matters, pica (particularly ice cravings) may also be a symptom, rather than a cause, of anemia.

Hookworm. Hookworm infects about 1 billion people worldwide and is a major cause of anemia in infested areas.

Impaired Absorption of Iron. Certain intestinal diseases (inflammatory bowel disease, celiac disease) or surgical procedures that affect the gastrointestinal tract can impair the ability of the intestine to absorb iron. (Such conditions also often impair folic acid absorption as well.)



Genetic Causes. Some people are born with iron deficiency. Certain cases may be due to a mutation of the Nramp2 gene, which regulates a protein responsible for delivering iron to the cells.

Anemia of Chronic Disease (ACD)

Anemia of chronic disease (ACD), also called anemia of chronic inflammation (ACI), is a common condition associated with a wide variety of persistent inflammatory diseases. It can be very severe and require transfusions.

The Inflammatory Process and ACD. ACD is not completely understood. In ACD, iron is not efficiently recycled from blood cells, and red blood cell survival is reduced. In addition, there is impaired response to erythropoietin, the hormone that acts in the bone marrow to increase the production of red blood cells. (Abnormal function and low levels of erythropoietin, in fact, may be the most important factor in ACD, with iron insufficiencies being a consequence.)

The process leading to ACD may occur in the following way:

- The immune system activates white blood cells and releases various compounds during times of infection that are intended to fight invaders and heal wounds. Such an event causes an inflammatory state in the areas of the attack.
- White blood cells called macrophages release small but powerful proteins known as *cytokines*, which are critical in the development of ACD. Cytokines are indispensable for healing. However, cytokines are overproduced often in chronic and inflammatory diseases, causing serious tissue injury and, in some cases, even organ damage. In the case of ACD, they prevent production of erythropoietin, the hormone that acts in the bone marrow to increase the production of red blood cells. Specific cytokines implicated in anemia are interleukin 1

(IL-1), tumor necrosis factor (TNF), and interferons.

- As part of this process, mechanisms prevent the release of recycled iron needed in the bone marrow for the manufacturing of red blood cells. Iron absorption in the intestines is also blocked. Theoretically, this is a protective measure, since iron may help infectious organisms proliferate. In such cases, iron stores are high, but the usable iron in circulation is low.
- Researchers have identified a peptide called hepcidin, which prevents iron absorption in the intestine and blocks the release of iron by immune factors for red blood cell production. Some experts believe high levels of the peptide may play a central role in preventing the release of iron during infection and inflammatory states, and is critical in ACD.

Diseases Associated with ACD and Inflammation. The chronic diseases that are associated with this process include:

- *Certain cancers*. Examples include lymphomas and Hodgkin's disease.
- *Autoimmune diseases*. Examples include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and polymyalgia rheumatica.
- *Long-term infections*. Examples include urinary tract infections and osteomyelitis. Common childhood infections, such as ear infections and urinary tract infections, may even cause anemia due to inflammation. (This anemia often resolves on its own but may be confused with iron deficiency.)
- *Hepatitis C*. The liver cirrhosis associated with hepatitis C can reduce the production of red blood cells. Gastrointestinal bleeding may also contribute to blood loss.
- *Heart failure*. Experts estimate that 25 – 60% of patients with heart failure also have anemia. However, it is unclear whether anemia actually causes or worsens heart failure. Recent research suggests it may actually be a sign (marker) of heart failure. Iron deficiency in heart failure can be due to a number of factors. It may be caused by a lack of nutrients in a person’s diet or by the body’s inability to absorb nutrients from food. Heart failure can also cause a back up of fluid (edema). This edema produces a higher volume of blood plasma (the liquid part of blood), which can dilute red blood cells and cause anemia.
- *Chronic kidney disease*. The hormone erythropoietin (EPO) is produced in the kidneys and stimulates the bone marrow production of red blood cells. Diseased kidneys do not release sufficient amounts of EPO; anemia can result and is universal in end-stage renal disease. Chronic kidney disease is a common complication of diabetes.
- *HIV/AIDS*. The inflammatory process associated with AIDS can adversely affect EPO levels and red blood cell production.
- *Anemia in critically ill patients*. Evidence suggests similarities between ACD and severe anemia in patients who are in intensive care. Some experts believe that the cause of anemia in such critically ill patients may also be due to inflammatory responses that promote impaired responsiveness to erythropoietin.

Not all chronic diseases involve the inflammatory process and anemia. For example, high blood pressure is a chronic disease, but it does not affect red blood cells.

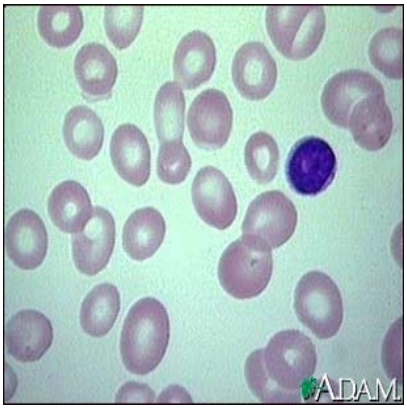
Treatment-Related Anemia. Anemia can also result from the therapies used to treat conditions. For example, anemia is a common side effect of cancer treatments. Chemotherapy and radiation can impair the bone marrow's production of red blood cells and contribute to the extreme fatigue that many patients experience during cancer therapy. Patients with hepatitis C frequently receive combination therapy of ribavirin and interferon; ribavirin can induce anemia. Hepatitis C also affects many patients with HIV or AIDS. In addition to ribavirin, patients with HIV or AIDS can develop anemia as a result of highly active anti-retroviral therapy (HAART) and, in particular, from the drug AZT.

Other medications that increase the risk for anemia are certain antibiotics, some antiseizure medications (phenytoin), immunosuppressive drugs (methotrexate, azathioprine), antiarrhythmic drugs (procainamide, quinidine), and anti-clotting drugs (aspirin, warfarin, heparin).

Megaloblastic Anemia

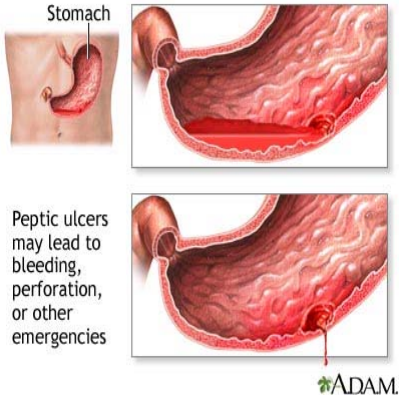
Megaloblastic anemia is the end-product of deficiencies in the B vitamins folate or vitamin B12 (also called cobalamin), or both. Such deficiencies produce abnormally large red blood cells (*megaloblastic*) that have a shortened life span. Neurologic problems are also associated with these deficiencies. Several conditions can

cause these deficiencies.



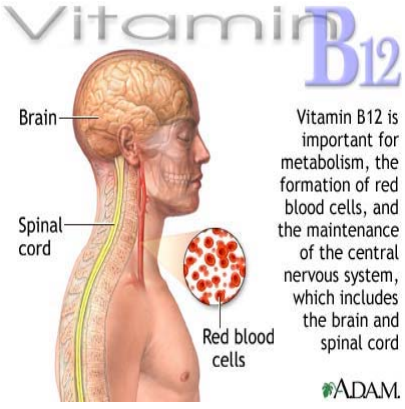
Causes of Vitamin B12 Deficiency. Conditions that cause vitamin B12 deficiencies include:

- Pernicious anemia. Pernicious anemia is an autoimmune disease in which antibodies are tricked into attacking stomach cells. This results in impaired production of intrinsic factor (IF), a compound that is critical for absorption of vitamin B12. Pernicious anemia is diagnosed in about 1% of people over age 60, with women having a higher risk than men.
- *H. pylori* and atrophic gastritis. A 2000 study suggested that the *H. pylori* bacterium is a player in many cases of vitamin B12 deficiency. These bacteria are not only major culprits in peptic ulcers but also are strongly associated with atrophic gastritis. This condition is a gradual loss of the stomach lining and is a known cause of vitamin B12 deficiency. (Some researchers theorize that H. pylori-induced injuries in the stomach lining may actually be the first step in the destructive process that leads to pernicious anemia.)



- Complications of gastrointestinal surgery. Surgeries such as stomach bypass or stapling, which remove part or all of the stomach, pose a 15 - 30% chance of causing vitamin B12 deficiencies.
- Overgrowth of intestinal bacteria
- Tropical sprue (an acquired malabsorption disease occurring in tropical climates)
- Overexposure to nitrous oxide

Vitamin B12 deficiency from diet is very rare, since the liver stores over a 3-year supply. It usually does not occur even in alcoholism, vegetarianism, or in malnourished people with kidney failure or cancer. Since animal products are the chief source, however, true vegan vegetarians may need a supplement, fortified food, or appropriate food selection known to contain adequate amounts of this vitamin.

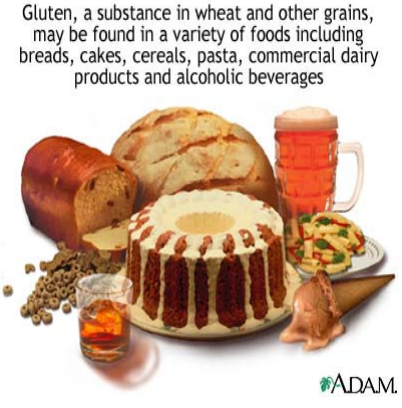


Causes of Folate Deficiency. The body stores only about 100 times its daily requirements for folate and can exhaust this supply within about 3 months if the diet is deficient in folate.

- Poor diet coupled with alcoholism is the most common cause of folate deficiency. Alcohol abuse not only contributes to malnutrition but also causes chemical changes that can result in lower folate levels.

Any condition that disturbs the small intestine and impairs its absorption ability can cause a deficiency. Such disorders include:

- Inflammatory bowel disease
- Celiac sprue (a sensitivity reaction to gluten)



- Parasitic diseases such as giardiasis
- Short bowel syndrome

Deficiencies can also arise due to high demand for folic acid caused by conditions such as cancer, pregnancy, severe psoriasis, severe hyperthyroidism, and hemolytic anemia. Some drugs, including Dilantin, methotrexate, trimethoprim, and triamterene, may also hinder folate absorption.

Less Common Anemias

Form of Anemia	Description and Diagnosis	Causes and Risk Factors	Treatments
Aplastic Anemia	Bone marrow fails to produce all types of blood cells.	Cause is unknown in half the cases. Known causes include hereditary	Transfusions, antibiotics, bone marrow or stem cell transplantation,

	Symptoms in addition to standard anemia are bleeding in mucous membranes and skin, gingivitis, higher risk for infection, and shortness of breath.	conditions (Fanconi's anemia), viruses (HIV, hepatitis, Epstein-Barr), autoimmune diseases (lupus, rheumatoid arthritis), medications (valproic acid, tacrolimus, azathioprine) or chemicals (benzene, pesticides).	immunosuppressant drugs. (This anemia used to be nearly always fatal, but survival rates now can reach 92% with successful transplants and up to 87% with immunosuppressants.)
Thalassemia	Genetic blood disease caused by a defect in the rate of production of hemoglobin. The two major forms are thalassemia minor and thalassemia major (Cooley's anemia, beta thalassemia). Thalassemia minor is the more common and milder form, in which life span is normal. Thalassemia major can be serious but it is fortunately very rare.	Affects males and females equally. Most common in people of Mediterranean descent, especially Italians and Greeks. Both types of thalassemia are found in an area that extends from northern Africa and southern Europe to Thailand, including Iran, Iraq, Indonesia, and southern China. Thalassemia major is more common in families who intermarry.	Transfusions to supply enough red blood cells to achieve moderate anemia and avoid iron overload are standard approaches for thalassemia major. Investigation ongoing to find alternatives to transfusions. Hydroxyurea may help some patients. Bone marrow transplantation may be needed. No treatment necessary for thalassemia minor.
Hemolytic Anemias: Acquired	Anemia caused by hemolysis (premature destruction of red blood cells). Diagnosis considered when there is marked increase in RBC production by bone marrow.	Autoimmune hemolytic anemia is the primary type, in which antibodies produced by the immune system damage RBCs. Cause unknown or associated with disorders such as systemic lupus erythematosus, lymphoma, and paroxysmal nocturnal hemoglobinuria. Other causes are high exposure to certain metals or chemicals (lead, copper, benzene, naphthalene), snake and insect bites, malaria, transfusions, post-surgical complications, and drugs such as methyldopa. In infants, blood group incompatibility between mother and child or infections in the womb.	Corticosteroids for autoimmune hemolytic anemia. Transfusions beneficial in many cases. An investigational drug, eculizumab, is showing promise in studies for paroxysmal nocturnal hemoglobinuria.

Hemolytic Anemias: Inherited	Hemolysis (premature destruction of RBCs) caused by sphere-shaped RBCs, which have difficulties circulating through the spleen.	Inherited defects include membrane defects, hemoglobin abnormalities, and enzyme deficiencies. Fava beans may trigger symptoms. More likely and more serious in males than females.	Blood transfusions may be necessary for some types of hemolytic anemia. Experimental trials use immune globulin. Removal of the spleen (splenectomy) or bone marrow transplantation may help some patients.
Sideroblastic Anemias	Group of anemias caused by impaired ability of bone marrow to produce normal RBCs. Normal to high iron levels, but iron cannot be used to make hemoglobin. In addition to the standard symptoms of anemia are jaundice, enlarged liver and spleen, fever, headache, loss of appetite, vomiting, and leg sores. Symptoms can be mild. Usually appears in childhood. Infections, trauma, and pregnancy may trigger symptoms.	Inherited or acquired after excessive alcohol use, certain medications, including chloramphenicol, or other disorders, including some cancers and rheumatoid arthritis. More common in the elderly.	Deferoxamine (Desferal) is used to remove iron. Effectiveness is increased when ascorbate is added to the regimen. Folate and pyridoxine are used, but their effectiveness is under question.
Sickle Cell Anemia	Serious, life-threatening, inherited disease. The sickle-shaped, inflexible RBC has impaired ability to squeeze through vessels. Short life span of RBC (10-20 days) causes anemia. In addition to anemia symptoms, joint and bone pain, infections, and heart failure can occur.	Disease occurs in 0.6% and the trait is found in the genetic makeup of 9% of African-Americans. Also occurs in people from India and Spanish-speaking and Mediterranean regions.	Measures to avoid cycling and control pain. Including hydration, hydroxyurea, NSAIDs and narcotic analgesics. Bone marrow transplantation. [See *In-Depth Report* #58: Sickle-cell disease.]

Risk Factors

Although nutritional iron-deficiency anemia has declined in industrialized nations, it affects an estimated 2 billion people worldwide. Even in the U.S., iron deficiency is the most prevalent nutritional deficiency. It is highly associated with poverty. People in lower socioeconomic groups have double the risk of those who are middle or upper class.

Among Americans with iron deficiency anemia, young children have the highest risk followed by premenopausal women. Adolescent and adult men and postmenopausal women have the lowest risk. Men, in fact, are at risk for iron overload, probably because of their higher meat intake.

General Risk Factors for Anemia in Infants and Children. Up to 20% of American children and 80% of children in developing countries become anemic at some point during their childhood and adolescence. Iron deficiency is the most common cause in children, but other forms of anemia, including hereditary blood disorders, can also cause anemia in this population. African-American children have the highest rates of anemia (about 25%) while other ethnic groups have an incidence under 20%.

Iron deficiency affects about 9% of children younger than 2 years. About 3% of children in this age group are anemic as a result. Children in lower-income homes are at higher risk than those in higher income homes. In a study of low-income children, ages 6 months to 5 years, the prevalence of anemia was over 10%, and was nearly 18% in children younger than 2 years. However, children in any income group can develop iron deficiency.

Young children 9 - 18 months have the highest risk for iron deficiency anemia in the U.S. Such children also are at great risk for problems in mental development from anemia. Infant boys may have 10 times more risk than baby girls. In general, full-term infants who are breastfed by their mothers have sufficient iron stores for their first 6 months of life. After that, they must rely on other sources for iron.

Iron-deficiency anemia in infants and small children can be due to one or more of the following factors:

- Stopping breast-feeding too early or using formula that isn't iron-fortified.
- Bottle-feeding too long. Studies indicate that the longer children are bottle-fed, the greater the risk for iron-deficiency and anemia. Toddlers 12 months and older should not drink more than 2 cups of milk a day. Cow's milk is good for children, but it does not contain enough iron. Too much milk can decrease children's appetite and prevent them from eating the iron-rich food they need. When babies who are bottle-fed are 7 - 9 months old, they should be weaned from bottles and given sippy cups. By the age of 12 months, all children should be using a cup instead of a bottle.
- Toddlers' preferences for iron-poor food. Parents should make sure that their children eat iron-rich foods such as beans, meat, fortified cereals, eggs, and green leafy vegetables

Better social services and more accurate ways of diagnosing and monitoring anemia are needed in these high-risk groups. There is still considerable debate on how to define iron deficiency and anemia in infants. New research suggests that a reticulocyte hemoglobin content (CHr) test may be better than a standard hemoglobin

test for detecting iron deficiency in babies. Reticulocytes are immature red blood cells. The CHr test measures the amount of hemoglobin in these cells.

Risk Factors for Anemia in Premenopausal Women. In a major government study, 9 - 16% of adolescent and adult women under 49 years were iron deficient. Hispanic American and African-American women had double the prevalence of Caucasian women. The risk for anemia in adolescent girls is about 3%. Anemia is generally mild in young women, however, and is more likely to occur with one or more of the following conditions:

- Heavy menstruation for longer than 5 days
- Abnormal uterine bleeding, such as from fibroids
- Pregnancy. About 20% of women in industrialized countries have iron deficiency during pregnancy. Multiple pregnancies and births significantly increase the risk.

Risk Factors for Anemia in Older Adults. Although studies have reported various estimates on the prevalence of anemia in older adults, one recent survey suggested that anemia affects approximately 10% of adults aged 65 years and older, and more than 20% aged 85 years and older. The causes of anemia in older adults were equally distributed among nutritional deficiencies, chronic inflammatory disease, chronic renal disease, and unexplained anemia. Most cases were mild.

People with Alcoholism

People with alcoholism are at risk for anemia both from internal bleeding and vitamin B deficiencies.

People with Iron-Poor Diets

Although most Americans probably consume too much iron in their diets, some people may be at risk for diet-related iron deficiencies:

- People whose diets are high in processed foods and lack any meat
- Strict vegetarians. Vegetarians who avoid all animal products may have a slightly higher risk for deficiencies in iron and some B vitamins. Although dried beans and green vegetables often contain iron, it is less easily absorbed from plants than from meat. Fortunately, most commercial cereals are fortified with vitamin B12 and folic acid (the synthetic form of folate).

Chronic or Critical Illnesses

Anyone with a chronic disease that causes inflammation or bleeding is at risk for anemia. Critical illness in the intensive care unit is also highly associated with anemia.

Athletes

Working out regularly may cause some iron loss, which is comparable to that from menstruation and rarely worrisome. One 2000 study suggests that dietary choices may account for most cases of sports anemia. Intense, sustained exercise, such as that performed by marathon runners, may cause a condition called sports anemia, which may be due to slight gastrointestinal bleeding, damaged red blood cells, low iron intake, or poor intestinal absorption of iron.

Anemia and the Pregnant Woman

Iron deficiency occurs in 20% of pregnant women in developed countries. Even worse, 50% or more of women in nonindustrialized nations become iron deficient, and between 30 - 50% are deficient in folic acid. Severe anemia is associated with a higher mortality rate among pregnant women. Mild-to-moderate anemia, however, does not pose any elevated risk.

Pregnancy increases the risk for anemia in different ways:

- It increases the body's demand for folic acid and, therefore, poses a risk for deficiencies and an increased risk

for megaloblastic anemia. Low levels of folate during pregnancy increase the risk of neural tube defects in newborns.

- It increases the body's demand for iron, thus posing a risk for iron deficiency anemia. Pregnant or nursing women require 30 mg of iron per day. Maternal iron deficiency anemia is associated with increased weight or size of the placenta, a condition that may later pose a risk for high blood pressure in the offspring. Pregnant women with low hemoglobin levels (the iron-bearing component in the blood) have an elevated risk for pre-term or low birth weight infants.
- Pregnancy is also associated with fluid retention, which in turn may produce high volumes of plasma (the fluid component of blood). This can dilute red blood cells, which may lead to anemia.
- After delivery, heavy bleeding, which occurs in 5 - 10% of women who have given birth, can cause symptoms of anemia.

Diagnosing of Iron Deficiency During Pregnancy

A diagnosis of iron deficiency is problematic in pregnant women. The standard test is a measurement of ferritin levels, which are low in most people with iron deficiency. Pregnant women, however, may have high ferritin blood levels into their third trimester but still be iron deficient. A newer test that measures a factor called serum transferrin receptor may prove to be a useful way of diagnosing iron deficiency in women. Researchers are also investigating Doppler ultrasonography as an imaging technique for detecting anemia in the fetus. Traditionally, fetal anemia is diagnosed through amniocentesis. Doppler ultrasonography is a non-invasive method that does not risk causing a miscarriage or a worsening of fetal anemia.

Preventing Anemia in Pregnant Women

Iron Supplements. For the past 40 years, iron supplements have been recommended for all pregnant women. This practice has been challenged recently, however. There is no clear-cut evidence that the mild iron deficiency in most pregnant women experience is harmful. In addition, iron supplements cause gastrointestinal side effects and may not be completely harmless.

Some experts suggest iron supplements for the following women:

- All pregnant women whose hemoglobin levels are less than 11 g/dl, and
- Pregnant women whose serum ferritin levels are low beginning in their 20th - 24th weeks of pregnancy.

Vitamin Supplements. Women who are trying to conceive, who are pregnant, and who are breastfeeding should take 400 mcg of folic acid a day. They should be sure this is folic acid and not folate. Folate is the natural form of folic acid, but 400 mcg supplements of folate are half as potent as the same dose of folic acid.

Pregnant and nursing women who are vegetarians should be sure to have supplements of folic acid and other B vitamins as well, since many of these nutrients are found primarily in animal products. Vitamin B12 deficiencies during pregnancy can also produce anemia in both mother and child.

Diets Rich in Vitamin C. Eating foods rich in vitamin C can help absorb iron.

Treating Anemia During Pregnancy

Pregnant women who become anemic and require treatment may be given oral iron supplements or transfusions in severe cases. Intravenous iron sucrose is a newer form of IV iron and may prove to be effective and safe for pregnant women with anemia.

Complications

Most cases of anemia are mild, including those that occur as a result of chronic disease. Nevertheless, even mild anemia can reduce oxygen transport in the blood, causing fatigue and a diminished physical capacity. Moderate to severe iron-deficiency anemia is known to reduce endurance. Some studies indicate that even iron deficiency *without* anemia can produce a subtle but still lower capacity for exercise.

Complications of Severe or Prolonged Anemia

Because a reduction in red blood cells decreases the ability to absorb oxygen from the lungs, serious problems can occur in prolonged and severe anemia that is not treated. Anemia can lead to secondary organ dysfunction or damage, including heart arrhythmia and heart failure.

Certain inherited forms of anemia, including thalassemia major, pernicious anemia, and sickle-cell anemia can be life-threatening. Thalassemia major and sickle-cell anemia affect children and are particularly devastating.

Effects of Anemia in Pregnant Women

Pregnant women who are anemic have an increased risk for poor pregnancy outcomes, particularly if they are anemic in the first trimester.

Complications from Anemia in Children and Adolescents

One study reported a higher incidence of ear infections in infants with iron deficiency anemia. Some experts have also identified an anemia in children that may be caused by inflammation from ear, urinary tract, and other infections.

In children, severe anemia can impair growth and motor and mental development. One small, well-conducted trial suggested that iron therapy in anemic children younger than 2 years may help reverse some of these problems. Iron deficiency in vegetarian children without anemia may cause mental impairment, but it appears to be temporary.

A long-term study reported that 11 - 15-year-old children who had been severely iron-deficient during their infant years scored lower than normal children cognitive and motor test scores, but particularly in written expression. They also tended to have more behavioral, general health, and emotional problems. Another study reported that teenage girls with iron deficiency, even without anemia, may have temporary memory and concentration loss.

Effects of Anemia in the Elderly

Anemia is common in older people and can have significantly more severe complications than anemia in younger adults. Some studies have reported higher mortality rates in anemic individuals 85 and older compared to their non-anemic peers. (The rates were higher in anemic men than in women.) The following are examples of its effects from different studies:

- Anemia may have adverse effects on the heart and increase the severity of cardiac conditions, including reducing survival rates from heart failure and heart attacks. Elderly patients who are anemic for more than 2 days before heart surgery may have a greater risk for complications and death.
- Anemia may predict the development of other serious problems. In one study, 13% of elderly people with anemia developed cancer over a 10-year period compared to 5% of non-anemic individuals. Rates of infection and peptic ulcer rates were also higher in anemic patients.
- Elderly people with lower levels of hemoglobin are at an increased risk of death.
- Anemia may be associated with an increased incidence of falls.
- There may be an association between anemia and vascular dementia. This form of dementia is caused by lack of oxygen to the brain and is not related to Alzheimer's disease. Even mild anemia may possibly lead to cognitive impairment. A 2006 study of elderly women found that mild anemia worsened problem-solving abilities and other cognitive functions.

Effects of Vitamin B12 Deficiencies and Pernicious Anemia

In addition to anemia, vitamin B12 deficiency can cause neurologic damage, which can be irreversible if it continues for long periods without treatment. In addition to being at risk for neurologic damage, people with pernicious anemia, which results in an inability to absorb vitamin B12, also have a higher risk for stomach cancer and possibly cancer of the throat and mouth.

Anemia in Patients with Cancer

Anemia is particularly serious in cancer patients. In people with many common cancers, the presence of anemia is associated with a shorter survival time. Anemia may worsen the toxicity of chemotherapy in elderly cancer patients.

Anemia in Patients with Kidney Disease

Anemia is associated with higher mortality rates and possibly heart disease in patients with kidney disease.

Anemia in Patients with Heart Failure

The combination of anemia and heart failure can increase the risk of hospitalization or death by 30 - 60%. Patients with heart failure whose hemoglobin levels decline do worse than patients with stable levels.

Effects of Excess Iron

Iron overload occurs when there is too much iron in the blood. It can be as serious a problem as iron deficiency. Iron overload is usually caused by:

- *Blood transfusions*. Patients with certain types of anemia require frequent blood transfusions. These transfusions can cause iron overload. Patients are treated with iron chelation therapy, which uses a drug that binds to iron. Excess iron is then eliminated by the kidneys. The standard drug for iron chelation therapy, deferoxamine (Desferal), is injected intravenously through an infusion pump. The treatment can be difficult for many patients. In 2005, a new drug, deferasirox (Exjade), was approved to treat iron overload due to blood transfusions. It is taken once a day by mouth. Patients dilute the pills in liquid and drink the mixture.
- *Hemochromatosis*. Hemochromatosis is a hereditary condition in which the intestinal tract absorbs too much iron from food. Over time this excess iron leads to damaged organs and joints. To reduce dangerous iron levels, blood is regularly removed from the patient's body. This procedure is called phlebotomy. It is similar to donating blood. Some patients also need iron chelation therapy. Deferoxamine is currently used for iron chelation therapy in patients with hemochromatosis. Researchers are investigating deferasirox for chelation treatment of this genetic condition.

Symptoms

Symptoms of anemia vary depending on the severity of the condition. Anemia may occur without symptoms and be detected only during a medical examination that includes a blood test. When they occur, symptoms may include:

- Weakness and fatigue are the most common symptoms of even mild anemia. Even iron deficiency without anemia can reduce working capacity in some people.
- Shortness of breath on exertion
- Rapid heartbeat
- Lightheadedness or dizziness
- Headache
- Ringing in the ears (tinnitus)
- Irritability and other mood disturbances
- Pale skin (however, healthy-looking skin color does not rule out anemia if a patient has risk factors and other symptoms of anemia)
- Iron deficiency, even at a level too mild to cause anemia, has been linked to restless legs syndrome (RLS) in some people. Some studies have reported RLS in 25 - 30% of people with low iron levels. Studies suggest, in fact, that RLS in some people may be due to impaired iron acquisition in cells that regulate dopamine in the brain. Dopamine abnormalities are known to play a role in RLS.
- Mental confusion
- Loss of sexual drive

Unusual Symptoms

Pica. One odd symptom, (which in some cases is a cause of iron deficiency), is *pica*. This is the habit of eating unusual substances, such as ice (called *pagophagia*), clay, cardboard, foods that crunch, or raw starch. For example, in one study, half of people whose pica took the form of pagophagia (eating at least one tray of ice every day for 2 months) or eating foods that crunch (such as raw potatoes, carrots, or celery) were iron deficient. The pica often stops, particularly in children, when iron supplements are given. Pica is difficult to detect because patients are often ashamed to admit to such cravings.

Frequent Breath Holding. Studies have also indicated that children who hold their breath frequently when angry or upset, even to the point of fainting, may be iron-deficient. In one study, taking iron supplements reduced this phenomenon in 88% of treated children.

Symptoms of Megaloblastic Anemia and its Causes

Symptoms of Megaloblastic Anemia. The symptoms of megaloblastic anemia from vitamin B12 or folic acid deficiencies include not only standard anemic symptoms but also:

- Inflammation of the mouth (*stomatitis*).
- Inflammation of the tongue (*glossitis*), which involves shrinkage at the surface and edges of the tongue

Over time, psychiatric and neurologic problems develop. Vitamin B12 deficiencies cause neurologic symptoms (numbness and tingling, depression, memory loss, and irritability), and folate deficiency may result in depression and dementia (in severe cases).

Symptoms of Pernicious Anemia. Early neurologic symptoms of pernicious anemia are due to B12 deficiency. They include numbness and tingling, depression, memory loss, and irritability. Advanced nerve damage can cause loss of balance and staggering, confusion, dementia, spasticity, loss of bladder control, and erectile dysfunction. Folic acid deficiency does not cause neurologic damage, although people with this deficiency can be irritable, forgetful, and experience personality changes. Of concern for patients with pernicious anemia and B12 deficiency anemia is that folic acid supplements can mask the presence of this disease in its early stages but not cure it. The only cure is vitamin B12 supplementation.

Diagnosis

The first step in any diagnosis is a physical examination to determine if the patient has symptoms of anemia and any complications. Because anemia may be the first symptom of a serious illness, determining its cause is very important. This may be difficult, particularly in the elderly, malnourished, or people with chronic diseases, whose anemia may be caused by one or more factors. A detailed medical, personal, and dietary history should report:

- Any family or personal history of anemia
- A history of gallbladder disease, jaundice, or enlarged spleen
- Heavy menstrual bleeding in women
- Any occurrence of blood in the stool or other signs of internal bleeding. (Even if the patient has not observed any bleeding, nonvisible blood may be present, so a rectal exam and stool test are essential.)
- Any dietary history, particularly in people who are elderly, poor, or both

The doctor should examine the patient carefully, especially checking for swollen lymph nodes, an enlarged spleen, and pale skin and nail color.

Blood Tests to Determine the Presence of Any Anemia

Specific blood tests are given to determine anemia from any cause.

Blood and Hemoglobin Counts. A complete blood count (CBC) test is performed to determine the presence of anemia. The red blood cells, or *erythrocytes*, and their iron-bearing component, *hemoglobin*, are measured.

For example, severe anemia in adults is defined by the World Health Organization as:

- Hemoglobin concentrations below 7.5 mmol/L (12 g/dL) in women. (Some evidence suggests that in older women anemia should be diagnosed at 13 g/dL and below.)
- Below 8.1 mmol/L (13 g/dL) in men.

A low red blood cell (RBC) count could indicate a number of problems, including bleeding or a failure by bone marrow to manufacture red blood cells.

Hematocrit. Calculating the percentage of red blood cells in blood *plasma* (a measurement called the *hematocrit*) is also important. Plasma is the liquid portion of blood. People with a high volume of plasma may be anemic even if their blood count is normal because the blood cells have become diluted.

Normal percentages are highest in the very youngest individuals and decline as people age. They also vary by gender. The following are some examples of normal range:

- Newborns: 42 - 60%
- Children: 35 - 45%
- Adult males: 41 - 53%
- Adult women: 36 - 46%

Normal value ranges may vary slightly among different laboratories.

Smokers, people at high altitudes, and those who are dehydrated tend to have higher than normal hematocrit levels. Those at greater risk for low hematocrit levels include pregnant women and patients with cirrhosis, heart failure, and splenomegaly.

Reticulocyte Count. Reticulocytes are immature red blood cells, and their count reflects the rate of red blood cell production. The upper normal limit is about 100,000/mL. A low count, when bleeding isn't the cause, suggests problems in production in the bone marrow. An abnormally high count indicates that the red blood cells are being destroyed in high numbers and indicates hemolytic anemia. New research suggests that the reticulocyte hemoglobin content (CHr) test may be more accurate than a standard hemoglobin test for detecting iron deficiency in infants. This test may help identify babies who are at risk for becoming anemic and help them get treated earlier.

Blood Morphology. A blood smear viewed under a microscope allows an expert to classify the blood by its color, size, and shape (its *morphology*). Generally red blood cells are categorized as:

- Pale-colored (*hypochromic*) and abnormally small (*microcytic*)
- Normal colored and normal sized (*normochromic*, *normocytic*)
- Abnormally large (*macrocytic*)

The shape of the red blood cells, which can be distorted in many blood disorders, is also important in determining a diagnosis.

Diagnosing Iron Deficiency Anemia and its Causes

There are two steps in making a diagnosis in patients with symptoms of iron deficiency anemia:

- The first step is to determine if a person is actually deficient in iron.
- If iron stores are low, the second step is to diagnose the cause of the iron deficiencies, which will help determine treatment.

Determining if Iron Stores are Low. The following findings are important in determining that a person is iron deficient:

- Blood cells viewed under the microscope are pale (*hypochromic*) and abnormally small (*microcytic*). They are also mostly uneven in shape. (These findings suggest iron deficiency, but they can also appear in cases of anemia due to chronic disease and thalassemia.)
- Hemoglobin and iron levels are low. (These findings further suggest iron deficiency, but they can also occur in

cases of anemia due to chronic disease.)

- Ferritin levels are low. Ferritin is a protein that binds to iron. Low levels typically mean reduced iron stores. High ferritin levels in the blood do not always mean sufficient iron stores. For example, pregnant women may have high ferritin levels into their third trimester but still be iron deficient. Ferritin levels may also be normal or even elevated in patients with inflammation from anemia due to chronic disease, even if they also have low iron stores.
- In children with iron deficiencies, *reticulocytehemoglobin* levels are low. Reticulocytes are immature red blood cells, and this test may be the most effective approach for diagnosing iron deficiency in children.
- A test that measures a factor called *serum transferrin receptor* (TfR) is proving to be very sensitive in identifying iron deficiency in problematic patients, including the elderly with chronic diseases and possibly pregnant women. (It is often very difficult to identify iron deficiencies in patients who also have anemia due to chronic diseases because their ferritin levels are often normal or even high.) For example, levels of TfR are high in patients with ACD and iron deficiency anemia, but they are normal or only slightly raised in ACD alone. The test is expensive, however, and some experts recommend it should be used only when there is a high suspicion of iron deficiency in the elderly.
- Measuring erythrocyte zinc protoporphyrin (ZPP), a product of abnormal heme synthesis, is under investigation and may prove to be a simple and precise measure of iron deficiencies, particularly in children.

Determining Causes of Iron Deficiency. When iron deficiency anemia is diagnosed, the next step is to determine what causes the iron deficiency itself.

- Dietary iron deficiency is most common in children and infants. It is rare in adults.
- Heavy menstrual or abnormal uterine bleeding is usually the cause of iron deficiencies in young women. Increased need for iron during pregnancy is also a common cause in this population.
- If internal bleeding is suspected as the cause, the gastrointestinal tract is usually the first suspect as the source. A diagnosis in these cases can often be made if the patient has noticed blood in the stools, which can be black and tarry or red-streaked. Often, however, bleeding may be present but not visible. If so, stool tests for this hidden (*occult*) blood are required. Additional tests may then be needed to diagnose the precipitating condition. Endoscopy, in which a fiber optic tube is used to view into the gastrointestinal tract, is helpful in many patients, particularly when the source of bleeding is unclear. A colonoscopy may also be recommended to rule out colorectal cancer.

If the patient's diet suggests low iron intake and other causes cannot be established using inexpensive or noninvasive techniques, then the patient may simply be given a monthly trial of iron supplements. If the patient fails to respond, further evaluation is needed.

Diagnosing Anemia of Chronic Disease (ACD)

Usually anemia of chronic disease is recognized during the management of the primary disease and, if the anemia is mild, additional diagnostic tests are rarely needed. The following are typical findings in ACD:

- The blood cells are normal looking.
- Blood tests may typically show low levels of iron in the blood, but ferritin levels are normal or even high. (Low levels of ferritin, a protein that binds to iron, indicate iron deficiency.)

Diagnosing Vitamin B-Related Anemias

Doctors need a multi-step diagnostic procedure for determining vitamin B deficiencies and the anemias that cause or are caused by them. Doctors may arrive at a diagnosis of vitamin B12 or folic acid deficiencies from different routes:

- They may diagnose deficiencies after detecting megaloblastic anemia from abnormal blood tests.
- They may suspect vitamin deficiencies first from symptoms and history and then look for anemia.

Diagnosing Megaloblastic Anemia. Very large oval red blood cells indicate megaloblastic anemia. Abnormally shaped neutrophils (certain white blood cells) may also be present. Bone marrow aspiration may need to be performed if the disease is strongly suspected but the diagnosis is not clear.

Determining Vitamin Deficiency. Once megaloblastic anemia has been diagnosed, the doctor will need to determine which vitamin deficiency is causing it. This is extremely important, because if a vitamin B12-deficient patient receives folate replacement only, then irreversible nerve injuries may develop. Even if blood tests for megaloblastic anemia are normal, patients with neurologic and psychiatric abnormalities that have no detectable cause should still be tested for vitamin B12 deficiency.

Deficiencies may be suggested by the presence of other disorders:

- Malnutrition, alcohol abuse, pregnancy, a history of sprue, severe psoriasis, or the use of antiseizure drugs may indicate a folic acid deficiency.
- A history of stomach surgery, eating raw fish (which raises the possibility of tapeworm), inflammatory bowel disease, or hypothyroidism suggests vitamin B12 deficiency.

Often, vitamin B deficiencies cannot be determined by a history or symptoms alone. Blood tests are the primary indicators of both vitamin B12 and folic acid deficiencies, but even blood tests for these vitamins are not always straightforward:

- Folic acid and vitamin B12 levels must always be measured at the same time because each vitamin may affect the other.
- Folate levels may be temporarily low in some people who are not truly deficient.
- Folate levels may temporarily rise in deficient people if they have just eaten foods containing the vitamin.
- Antibiotics can interfere with B12 levels.

Measuring methylmalonic acid and homocysteine, substances in the blood that increase when levels of one or both vitamins are low, improves accuracy.

Tests for Pernicious Anemia. Once a vitamin B12 deficiency has been established and the doctor has not found any intestinal abnormalities or other factors to account for the deficiency, the doctor presumes a diagnosis of pernicious anemia. Pernicious anemia may also be diagnosed through various blood (such as complete blood count) or urine tests.

Pernicious anemia is treated with vitamin replacement, but the condition is easily missed, particularly in patients whose diets are rich in folic acid. Folic acid can mask the early symptoms of pernicious anemia but not cure it. Consequently the disease may persist until serious neurologic symptoms occur. With folic acid now a required additive in many commercial foods, some experts are concerned about an increased incidence in pernicious anemia.

Dietary Factors

Iron found in foods is either in the form of heme or non-heme iron:

- *Heme Iron*. Foods containing heme iron are the best sources for increasing or maintaining healthy iron levels. Such foods include (in decreasing order of iron-richness) clams, oysters, organ meats, beef, pork, poultry, and fish.
- *Non-Heme Iron*. Non-heme iron is less well-absorbed. About 60% of the iron in meat is non-heme (although meat itself helps absorb non-heme iron). Eggs, dairy products, and iron-containing vegetables have *only* the non-heme form. Such vegetable products include dried beans and peas, iron-fortified cereals, bread, and pasta products, dark green leafy vegetables (chard, spinach, mustard greens, kale), dried fruits, nuts, and seeds.

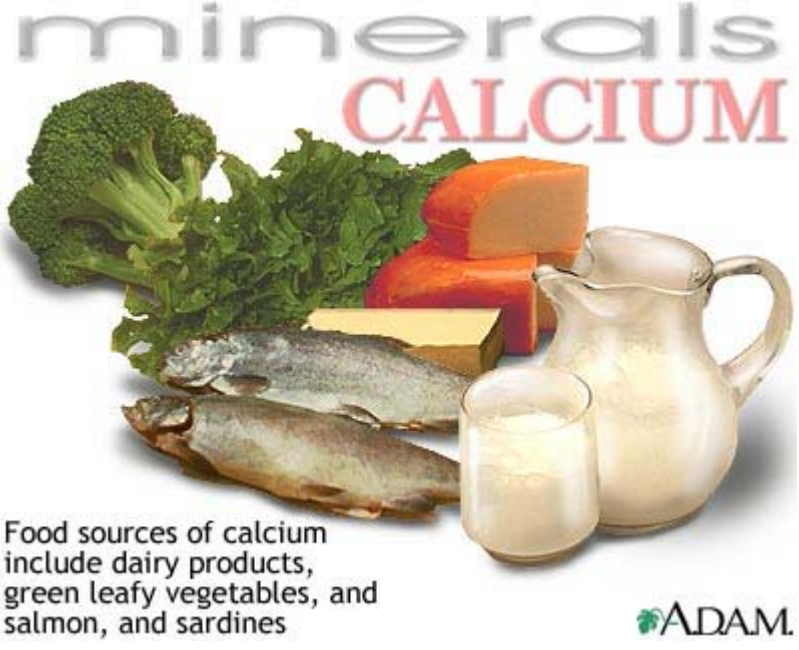
The absorption of non-heme iron often depends on the food balances in meals. The following foods and cooking methods can enhance absorption of iron:

- Meat and fish not only contain heme iron -- the best form for maintaining stores -- but they also help absorb non-heme iron.
- Increasing intake of vitamin-C rich foods, such as orange juice, may enhance absorption of non-heme iron, although it is not clear if it improves iron stores in iron-deficient people. In any case, vitamin-C rich foods are healthy and include broccoli, cabbage, citrus fruits, melon, tomatoes, and strawberries.

- Riboflavin (vitamin B2) may help enhance the response of hemoglobin to iron. Food sources include dairy products, liver, and dried fortified cereals.
- Cooking methods can enhance iron stores. Cooking in cast iron pans and skillets is well-known to increase the iron content of food. According to one study, boiling, steaming, or stir-frying in utensils composed of *any* material significantly increased the release of non-heme iron stored in vegetables.

Certain nutrients *interfere with* the body's absorption of dietary iron. They include:

- Polyphenols (found in tea, coffee, red wine, berries, apples)
- Phytates (found in foods such as seeds, dried beans, soy, and bran). Such foods are typically high in fiber. (It is often believed that fiber itself impedes iron absorption, but researchers report that it has little or no effect.)
- Calcium. Calcium impairs the absorption of heme and non-heme iron. However, calcium intake must be quite high to cause any significant problems. For example, a 2002 study reported that cheese had no effect on iron absorption from meals rich in heme and non-heme iron.

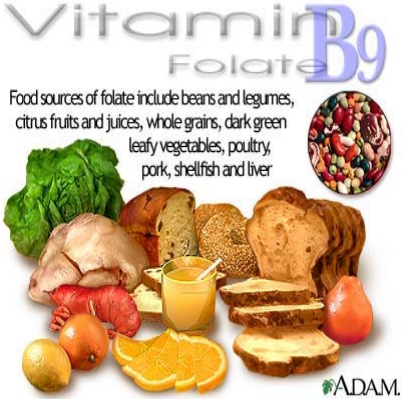


Getting enough calcium to keep bones from thinning throughout a person's life may be made more difficult if that person has lactose intolerance or another reason, such as a tendency toward kidney stones, for avoiding calcium-rich food sources. Calcium deficiency also affects the heart and circulatory system, as well as the secretion of essential hormones. There are many ways to supplement calcium, including a growing number of fortified foods.

Sources of Vitamins B12 and Folate. Vitamins B12 and folate are important for prevention of megaloblastic anemia and for good health in general.

- The only natural dietary sources of B12 are animal products, such as meats, dairy products, eggs, and fish (clams and oily fish are very high in B12). As is the case with other B vitamins, however, B12 is added to commercial dried cereals. The recommended daily allowance (RDA) is 2.4 mcg a day. Deficiencies are rare in young people, although the elderly may have trouble absorbing natural vitamin B12 and require synthetic forms from supplements and fortified foods.

- Folate is best found in avocado, bananas, orange juice, cold cereal, asparagus, fruits, green, leafy vegetables, dried beans and peas, and yeast. The synthetic form, folic acid, is now added to commercial grain products. Vitamins are usually made from folic acid, which is about twice as potent as folate. Many experts now recommend that adults have 400 mcg of folic acid daily -- considerably higher than standard recommendations of 400 mcg of *folate*. Women who are trying to conceive, who are pregnant, and who are breastfeeding should take 400 mcg of folic acid.



Recommended Daily Allowance for Iron

The Recommended Daily Allowance (RDA) of iron for people who are not iron deficient varies by age group and other risk factors. (Iron supplements are rarely recommended in people without evidence of iron deficiency or anemia.) The RDA recommends these daily amounts of iron:

- Children 1 - 3 years old: 10 mg
- Teenage boys: 12 mg
- Teenage girls and premenopausal women: 15 mg
- Pregnant or nursing women: 30 mg
- Adult men (up to age 50): 10 mg
- Older men and women (over age 50): 10 mg

Preventing Anemia in Infants and Small Children

The main source of iron for an infant from birth to 1 year of age is in milk, either from breast milk, iron-fortified infant formula, or cereal. The best methods for preventing iron deficiency during infancy are:

Breastfeeding and Iron-Supplemented Formulas. Mothers should be encouraged to breastfeed their babies for their first year. Up to half of the iron in breast milk is absorbed by the baby and is sufficient to prevent anemia for the first 4 - 6 months, assuming that the mother had adequate iron stores during pregnancy. Breast milk

itself is low in iron, but if the mother's diet is healthy, vitamin C and lactose in the breast milk may enhance iron absorption. Breastfed babies should have iron supplements after 4 - 6 weeks, even if they are still nursing.

Infants who are not breastfed should start with iron-fortified formulas. Most experts strongly discourage the use of low-iron formulas (less than 4.0 mg/L). However, a 2002 study suggested that formulas with iron levels as low as 1.6 mg Fe/L provide sufficient iron to infants and higher amounts do not add any benefit. Parents should discuss the best formula with their doctor. Children given iron supplements may have a slightly higher risk for diarrhea. Experts advise against cow's milk for the first year of life.

Recommendations for Toddlers. Toddlers who did not have iron supplements during infancy should be checked for iron deficiency. After the first year, children should be given a varied diet that is rich in sources of iron, B vitamins, and vitamin C. Milk does not contain enough iron and can decrease children's appetite for iron-rich foods. Toddlers older than 1 year should not drink more than 2 cups of milk a day. A preference for apple juice over vitamin-C rich orange juice does not reduce iron absorption in children with any otherwise healthy diet.

Treatment

Oral iron supplements are the best way to restore iron levels for people who are iron deficient, but they should be used only when dietary measures have failed. However, iron supplements cannot correct anemias that are not due to iron deficiency.

One study reported that doctors prescribed iron pills for 64% of patients with anemia without performing tests to confirm whether iron deficiency was actually the cause. The study suggested that iron replacement was appropriate in less than half of these patients. Iron replacement therapy can cause gastrointestinal problems, sometimes severe ones. Excess iron may also contribute to heart disease, diabetes, and certain cancers. Experts generally advice against iron supplements in anyone with a healthy diet and no indications of iron deficiency anemia. However, a 2003 study suggested that supplements help reduce fatigue in women with low iron stores but no signs of anemia.

Treatment of Anemia of Chronic Disease. In general, the best treatment for anemia of chronic diseases is treating the disease itself. In some cases, iron deficiency accompanies the condition and requires iron replacement. Erythropoietin, most often administered with intravenous iron, is used for some patients.

Treatment of Megaloblastic Anemia. The standard treatments for megaloblastic anemia are vitamin B12 injections and folic acid replacement.

Iron Supplements

Supplement Forms. To replace iron, the preferred forms of iron tablets are ferrous salts, usually ferrous sulfate (Feosol, Fer-In-Sol, Mol-Iron). Other forms include ferrous fumarate (Femiron, FerroSequels, Feostat, Fumerin, Hemocyte, Ircon), ferrous gluconate (Fergon, Ferralet, Simron), polysaccharide-iron complex (Niferex, Nu-Iron), and carbonyl iron (Elemental Iron, Feosol Caplet, Ferra-Cap). Specific brands and forms may have certain advantages. The following are some examples:

- Prolonged-release ferrous sulfate (Slow Fe) may enhance iron absorption with fewer side effects than standard ferrous sulfate pills.
- FerroSequels contains a stool softener, which helps prevent constipation.
- Polysaccharide-iron complex has fewer side effects and equal absorption rates compared to ferrous salts. It is very expensive, however.
- Carbonyl iron is composed of very fine tiny uniform spheres of iron powder and may prove to be less toxic than ferrous iron.
- Coated or combination pills do not appear to offer any additional advantages and may hinder absorption of the iron.

Regimen. The general guidelines for iron replacement are as follows:

- For adults, doctors usually advise one ferrous sulfate tablet (300 mg) three times a day.

- Iron replacement doses for children with deficiencies are significantly lower. In general, they are given as drops or syrup administered three times a day. A single-dose daily regimen is showing promise. *IMPORTANT: As few as three adult iron tablets can poison children, even fatally. This includes any form of iron pill.*
- No one, even adults, should take a double dose of iron if one is missed.

Other tips for taking iron are as follows:

- For best absorption, iron should be taken between meals. (Iron may cause stomach and intestinal disturbances, however, and some experts believe that low doses of ferrous sulfate can be taken with food and are still absorbed but with fewer side effects.)
- Always drink a full 8 ounces of fluid with an iron pill. Taking orange juice with an iron pill may help increase iron absorption. (Some doctors also recommend taking a vitamin C supplement with the iron pill.)
- Tablets should be kept in a cool place. (Bathroom medicine cabinets may be too warm and humid, which may cause the pills to disintegrate.)

Full recovery takes 6 - 8 weeks. Recovery will take longer in people with internal bleeding that is not under control. Iron replacement therapy must continue for about 6 months, even if anemia has been reversed. Treatment must be continued indefinitely for people with chronic bleeding; in such cases, iron levels should be closely monitored.

Side Effects. Common side effects of iron supplements include the following:

- Constipation and diarrhea are very common. They are rarely severe, although iron tablets can aggravate existing gastrointestinal problems such as ulcers and ulcerative colitis.
- Nausea and vomiting may occur with high doses, but can be controlled by taking smaller amounts. Switching to ferrous gluconate may help some people with severe gastrointestinal problems.
- Black stools are normal when taking iron tablets. In fact, if they do not turn black, the tablets may not be working effectively. This tends to be a more common problem with coated or long-acting iron tablets.
- If the stools are tarry looking as well as black, if they have red streaks, or if cramps, sharp pains, or soreness in the stomach occur, gastrointestinal bleeding may be causing the iron deficiency and the patient should call the doctor promptly.
- Acute iron poisoning is rare in adults but can be fatal in children who take adult-strength tablets.

Interactions with Other Drugs. Certain medications, including antacids, can reduce iron absorption. Iron tablets may also reduce the effectiveness of other drugs, including the antibiotics tetracycline, penicillamine, and ciprofloxacin and the Parkinson's disease drugs methyldopa, levodopa, and carbidopa. At least 2 hours should elapse between doses of these drugs and iron supplements.

Supplements. The following vitamin and mineral supplements may improve iron absorption:

- Adding either ascorbic acid (vitamin C) or succinic acid to ferrous sulfate therapy will improve absorption of iron stores.
- Some studies have found that the addition of zinc to iron supplements increases hemoglobin levels more than iron alone. Some evidence for this suggests that zinc affects a hormone called insulin-like growth factor-I (IGF-I), which plays a role in the regulation of red blood cell production.

Intravenous or Injected Iron

In some cases, iron is administered through muscular injections or intravenously. Intravenous iron has the advantage of causing less gastrointestinal discomfort and inconvenience. It may be in the form of iron dextran (Dexferrum, InFed), sodium ferric gluconate complex in sucrose (Ferrlecit), or iron sucrose (Venofer). Ferrlecit or Venofer are proving to be at least equally effective and safer than iron dextran.

Candidates. The injected or intravenous forms should be limited to the following patients with iron deficiency:

- People with iron deficiency anemia in whom oral therapy has clearly failed.
- Patients with bleeding disorders in which blood loss continues to exceed the rate at which oral iron is absorbed.
- In emergencies, when people need red blood cells but transfusion is not appropriate or available.

- In people with serious gastrointestinal disorders, such as inflammatory bowel disease, who cannot take iron therapy by mouth.
- People undergoing hemodialysis who receive supplemental erythropoietin therapy. Sodium ferric gluconate complex in sucrose (Ferrlecit) or iron sucrose (Venofer) is specifically approved as first-line therapy for these patients. One 2003 study suggested that a combination of iron and vitamin C by mouth might be sufficient to maintain adequate iron and vitamin C stores.

Certain patients, even if they meet these qualifications, may not be appropriate candidates or should be monitored closely for complications. They include:

- Patients with any underlying autoimmune disease.
- Malnourished patients who also have an underlying infection.
- Patients who are at risk for iron overload.

Side Effects. Some side effects differ depending on how the iron is administered and include the following:

- Muscular injections include pain at the site.
- Intravenous administration can cause pain in the vein, flushing, and metallic taste, all of which are brief.

For both methods, side effects and serious complications can include:

- Blood clots
- Fever
- Joint aches
- Headache
- Rashes
- A delayed reaction of joint and muscle aches, headache, and malaise occurs 1 - 2 days after the infusion (most commonly with iron dextran) in about 10% of patients. These symptoms respond quickly to NSAIDs, such as ibuprofen or naproxen, in most people.
- Iron toxicity. Symptoms include nausea, dizziness, and a sudden drop in blood pressure. Sodium ferric gluconate in sucrose (Ferrlecit) or iron sucrose (Venofer) may pose a lower risk for toxicity than iron dextran.
- Allergic reactions. Allergic reactions that occur with intravenous iron can be very serious and, in rare cases, even fatal. Iron dextran appears to pose a much higher risk than sodium ferric gluconate complex in sucrose or iron sucrose, although allergic reactions can also occur with the latter forms.

Oral and injected iron should *never* be given at the same time. Intravenous iron therapy may be appropriate for some pregnant women who meet these requirements, depending on the pregnancy term and other factors.

Transfusions and Bloodless Medicine

Transfusions are used to replace blood loss due to injuries and during certain surgeries. They are also commonly used to treat severely anemic patients who have thalassemia, sickle cell disease, myelodysplastic syndromes, or other types of anemia. Some patients require frequent blood transfusions. Iron overload can be a side effect of these frequent blood transfusions. If left untreated, iron overload can lead to liver and heart damage.

Iron chelation therapy is used to remove the excess iron caused by blood transfusions. Patients take a drug that binds to the iron in the blood. The excess iron is then removed from the body by the kidneys. For many years, deferoxamine (Desferal) was the only drug used in chelation therapy. This drug is usually injected intravenously, using an infusion pump. The infusion can last 8 - 12 hours and may be needed 5 - 7 days a week until iron levels are normal. A new drug, deferasirox (Exjade), was approved in 2005 for children and adults as a once-daily treatment for iron overload due to blood transfusions. It does not require injections. Patients mix the deferasirox tablets in liquid and drink the medicine. Doctors hope that this new drug may make it easier for patients to tolerate chelation therapy. Studies have shown that deferasirox works as well as deferoxamine in ridding the body of excess iron.

Bloodless Medicine. Bloodless medicine and surgery is a new field designed to reduce or minimize blood loss and transfusions. It also attempts to address the problems in treating certain religious groups, such as

Jehovah's Witnesses, who refuse transfusions. Some techniques involved in this field include new surgical procedures or drugs that minimize blood loss, the use of erythropoietin, volume expanders (administration of fluids to dilute blood), using tiny blood samples for testing, and methods (Cell Saver) for recovering and recycling blood during surgery.

Erythropoiesis-Stimulating Drugs

Erythropoietin is the hormone that acts in the bone marrow to increase the production of red blood cells. It has been genetically engineered as recombinant human erythropoietin (rHuEPO) and is available as epoetin alfa (Epogen, Procrit, and Eprex). Novel erythropoiesis stimulating protein (NESP), also called darbepoetin alfa (Aranesp), lasts longer in the blood than epoetin alfa and requires fewer injections. These medications are also called “erythropoiesis-stimulating drugs.”

Levels of erythropoietin are reduced in anemia of chronic disease. Injections of synthetic erythropoietin can help reduce the need for blood transfusions and improve quality of life measures. Erythropoietin is currently used for treating patients with anemia related to the following conditions:

- Chronic kidney disease and diabetes. Erythropoietin is an important treatment for patients on dialysis and has proven to reduce the risk of death from heart disease and improve quality of life.
- Cancer. Erythropoietin is administered to manage the anemia associated with chemotherapy and other cancer treatments.
- Chronic heart failure. Erythropoietin and intravenous iron may improve cardiac and renal (kidney) function.
- Myelodysplastic syndromes (MDS). MDS is a blood and bone marrow disease that is related to leukemia. In MDS, the bone marrow does not produce enough blood cells. Patients require frequent blood transfusions, which can lead to anemia. Erythropoietin is given to produce more red blood cells along with drugs that stimulate white blood cells. Darbepoetin alfa (Aranesp) is also showing promise in treating the anemia associated with MDS
- Rheumatoid arthritis (RA). Erythropoietin may be used in combination with intravenous iron supplementation to treat both adult and juvenile RA.
- Inflammatory bowel disease. Erythropoietin plus iron supplementation can be beneficial for treating anemia associated with Crohn's disease and ulcerative colitis.
- Hepatitis C. Erythropoietin may mitigate the effects of ribavirin-induced anemia.
- HIV/AIDS. HIV-positive patients may develop anemia as a side effect of treatment with AZT or ribavirin (for co-infection with hepatitis C). Recent research has indicated that weekly injections of epoetin alfa may be as effective as a three times per week regimen.

Although these drugs are used to treat anemia, they can sometimes cause severe anemia. If patients taking these drugs do develop severe anemia, the doctor will immediately stop drug treatment. The risk of drug-caused anemia is greatest for patients with chronic kidney failure who receive these drugs through under-the-skin injections. To reduce the risk of anemia, epoetin alfa and darbepoetin alfa should be given intravenously to patients on dialysis.

Dosing target levels of erythropoiesis-stimulating drugs are controversial, especially for patients with chronic kidney disease. In 2006, two important *New England Journal of Medicine* (*NEJM*) studies indicated that aggressive dosing to completely normalize hemoglobin levels does not work better than standard dosing that only partially corrects anemia. In addition, the higher dosing approach was associated with increased risk for serious cardiovascular events including heart failure, heart attack, and fatal stroke.

In response to these *NEJM* studies, the FDA issued the following warnings to doctors and patients:

- Erythropoiesis-stimulating drugs should be used to maintain hemoglobin levels of between 10 - 12 g/dL. (The *NEJM* studies found that patients dosed to hemoglobin target levels of 13.5 g/dL had a greater risk of serious heart problems than patients whose levels did not exceed 12 g/dL.)
- Patients who take these drugs should receive frequent blood tests to monitor their hemoglobin levels, to make sure they are in a safe range.
- Patients should immediately contact their doctors if they experience worsening in shortness of breath, pain, swelling in the legs, or increases in blood pressure.

Epoetin may increase the risk for blood clots. Some experts are also concerned that certain patients may develop antibodies that react against epoetin. This may be more of a problem with some brands (Eprex) than others.

Antibiotics for *H. Pylori*

H. pylori, the bacteria that cause peptic ulcers, is associated with anemias from vitamin B12 deficiency and iron deficiency. People whose anemia is associated with *H. pylori* infection, however, do not respond to iron therapy. Studies indicate that the eradication of *H. pylori i*nfection with antibiotics can reverse anemia in such patients and may lead to long-lasting recovery.

Vitamin Replacement for Megaloblastic Anemia

Vitamin B12 Therapy. Injections of vitamin B12 (usually formulations called cyanocobalamin or hydroxocobalamin), oral folic acid therapy, or both, rapidly reverse the production of abnormally large red blood cells. (Treatments still may not reverse neurologic symptoms if they are extensive or have continued for too long.)

A typical regimen for vitamin B12 replacement is as follows:

- If diagnostic tests indicate pernicious anemia and neurologic symptoms are present, vitamin B12 therapy should begin immediately. (Usually vitamin therapy is not an emergency, however.)
- Cyanocobalamin or hydroxocobalamin injections are given every day for up to 2 weeks. Only small doses are needed.
- This is followed by injections twice a week for another month. (Hemoglobin levels rise in the first week of therapy and reach normal levels in 8 weeks.)
- After that, injections are usually given monthly.
- During recovery, there is a risk of potassium deficiency as the new red cells take up the existing supply, so potassium supplements may be needed.

Other forms of vitamin B12 are also available and can be used to treat B12 deficiency. Vitamin B12 nasal spray offers the same advantage of avoiding the need for absorbing the vitamin in the GI tract without the inconvenience of the injections. Some experts feel that even oral B12 in high doses (2,000 mcg/day) can maintain B12 levels once the deficiency is treated.

The injections are safe and have no adverse side effects, but they may mask an underlying medical or psychological condition.

Some doctors give vitamin B12 injections for fatigue and other vague symptoms of general mild discomfort. In one study, 10% of patients in a rural clinic were given regular B12 shots, with 6% of patients having no medical need for them.

Folic Acid Treatment. Folate deficiency is easily remedied in 4 - 5 weeks with daily oral doses of 1 - 2 milligrams of folic acid. Many doctors give vitamin B12 along with folic acid unless B12 deficiency is definitely ruled out.

Resources

- www.anemia.org -- National Anemia Action Council
- www.nhlbi.nih.gov -- National Heart, Lung and Blood Institute
- www.irondisorders.org -- Iron Disorders Institute
- www.thalassemia.org -- Cooley's Anemia Foundation
- www.aamds.org -- Aplastic Anemia & MDS International Foundation
- http://kidney.niddk.nih.gov/kudiseases/pubs/anemia -- National Kidney and Urologic Diseases Clearinghouse (Anemia in kidney disease and dialysis)

References

Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. *Blood*. 2006 May 1;107(9):3455-62.

Chaves PH, Carlson MC, Ferrucci L, Guralnik JM, Semba R, Fried LP. Association between mild anemia and executive function impairment in community-dwelling older women: The Women's Health and Aging Study II. *J Am Geriatr Soc*. 2006 Sep;54(9):1429-35.

Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006 Nov 16;355(20):2071-84.

Hillmen P, Young NS, Schubert J, Brodsky RA, Socie G, Muus P, Roth A, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006 Sep 21;355(12):1233-43.

Oepkes D, Seaward PG, Vandenbussche FP, Windrim R, Kingdom J, Beyene J, et al. Doppler ultrasonography versus amniocentesis to predict fetal anemia. *N Engl J Med*. 2006 Jul 13;355(2):156-64.

Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006 Nov 16;355(20):2085-98.

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Special Instructions: