Anemia

Anemia is defined as ‘a pathologic deficiency in the amount of oxygen-carrying hemoglobin in the red blood cells.’ Anemia is having less than the normal number of red blood cells or less hemoglobin than normal in the blood.

Symptoms

It is a common problem for cancer patients and often results from the therapies used to suppress or control tumors. Anemia is associated with fatigue - a feeling of weakness or diminished physical and mental capacity unrelieved by rest (fatigue). Additional symptoms include diminished ability to perform daily functions and possibly impaired cognitive function, headache, dizziness, chest pain and shortness of breath, nausea, depression and occasionally pain. These symptoms are often complicated by coexisting disease(s). There are many compromises that are necessary when one has symptomatic anemia. This can affect the tolerability of therapy. Anemia is also associated with a poorer prognosis and increased mortality.

Causes of Anemia

- **Blood loss**: excessive bleeding such as hemorrhages or abnormal menstrual bleeding
- **Chronic illness** secondary to refractory anemia: inflammatory GI/GU diseases, malignancies (cancer), arthritis, kidney or liver failure, and acute and chronic infections
- **Cancer therapy**: surgery, radiotherapy, chemotherapy and/or immunotherapy
- **Infiltration** (replacement) of bone marrow with cancer
- **Hemolysis**: Breakdown or destruction of red blood cells
• *Decreased red cell production* due to low levels of erythropoietin (a hormone produced by the kidney {90%} and liver {10%}) which promotes red blood cell production.

There is no one cause of anemia.

**Red Blood Cells**

Anemia is usually detected or at least confirmed by a complete blood cell (CBC) count.

In a CBC test, the different types of cells in the blood are counted and examined. Today, much of this work is often automated and done by machine. Six tests make up a CBC:

- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- White blood cell (WBC) count
Differential blood count

Platelet count

Only the first three of these tests: the red blood cell (RBC) count, the hematocrit, and the hemoglobin, are relevant to the diagnosis of anemia.

The red blood cells (RBCs) are the most common type of cells in the blood. Everyone has millions and millions of these little disc-shaped cells. The RBC count is done to determine if the number of red blood cells is low (anemia) or high (polycythemia).

In an RBC count, the number and size of the RBCs are determined. The shape of the red blood cells is also evaluated under a microscope. All of this information, the number, size and shape of the RBCs, is useful in the diagnosis of anemia and, if there is anemia, in the decision about the exact type of anemia.

The hematocrit is a very convenient way to determine whether the red blood cell count is too high, too low, or normal. The hematocrit is specifically a measure of how much of the blood is made of red cells.

Hemoglobin is a red pigment; it imparts the familiar red color to red blood cells and to blood. Functionally, hemoglobin is the key chemical compound that combines with oxygen from the lungs and carries the oxygen from the lungs to cells throughout the body. Oxygen is essential for cells to produce energy. The blood also transports carbon dioxide, which is the waste product of this energy production process, back to the lungs from which it is exhaled into the air.

The tests usually done to access anemia include:

(1) Hemoglobin and hematocrit
(2) Reticulocyte count - counts number of early red cells being produced and released from bone-marrow.
(3) A Coombs antibody test, direct and indirect antibodies
(4) Serum haptoglobins to detect hemolysis
(5) Enzymatic deficiencies with secondary drug sensitivity (allergy), such as G6PD, pyruvate kinase enzyme deficiencies.

Low hemoglobin level

People with a low hemoglobin level have anemia. When there is a low hemoglobin level, there is often a low red blood cell count and a low hematocrit, too.

Oxygen transport through the body is subnormal. The person with anemia is under oxygenated. Because of this people with anemia can feel tired, fatigue easily, appear pale, develop palpitations, and become short of breath.

Treatments

The treatment of the anemia varies greatly. The successful treatment of anemia depends on identifying and treating the underlying cause. Through laboratory test results and a physical examination, determine the cause of anemia and identify the best approach to treating it.

For example, anemia as a result of blood loss from a stomach ulcer should begin with medications to heal the ulcer. Likewise, surgery is often necessary to remove a colon cancer that is causing chronic blood loss and anemia. Sometimes iron supplements will also be needed to correct iron deficiency. Sometimes blood transfusions are necessary. Vitamin B12 injections will be necessary for patients suffering from pernicious anemia or other causes of B12 deficiency. In certain patients with bone marrow disease (or bone marrow damage from chemotherapy) or patients with kidney failure, epoetin alfa (Procrit, Epogen) may be used to stimulate bone marrow red blood cell production.

Blood transfusions providing red blood cell transfusions for bleeding and/or severe chronic anemia may be lifesaving. Red cell transfusions are the old mainstay, which offers the quickest relief for anemia.
Risks associated with transfusions.

- Allergic reactions
- Transmissions of infectious agents (hepatitis, HIV)
- HBV (hepatitis B virus)
- HIV (AIDS)
- HIV 2
- HTLV (Human Leukemia Virus)
- Immune suppression
- Iron overload from multiple transfusions (usually over 25-50 units of red cells).
- When patients with megaloblastic anemia receive a transfusion of red blood cells, the platelet count, for unknown reasons, decreases by about 50%. If the pre-transfusion platelet count is low—say, 30,000/mm³—the decrease could result in serious bleeding.

It is better to avoid transfusion unless absolutely necessary.

[The viral risks of blood transfusions have recently been reduced due to a more accurate blood test called NAT (Nucleic Acid Test). This tests specifically for evidence of HIV and hepatitis C virus (HCV).]

Four Types of Anemias

1. Iron deficiency due to iron loss. This is usually from a GI site with gastrointestinal bleeding. This is rarely from a nutritional deficiency, and in such cases, it usually takes over 10-20 years to develop.

2. Anemia of deficiencies such as:
   (a) Vitamin B12 deficiency,
   (b) folic acid deficiency,
   (c) rarely copper or mineral deficiencies.
3. Production problems with anemia usually secondary to a disease process, as
   (a) Chronic or acute infections or inflammation,
   (b) hematological problems such as leukemia, lymphoma, usually involving the bone marrow,
   (c) cancer,
   (d) Inflammatory diseases such as lupus or arthritis,
   (e) Chronic illness.
4. Hemolysis (a shortening of red cell survival), hemolytic anemias as in
   (a) Non-immune hemolytic anemias such as sickle cell, haemoglobinopathies, spherocytosis, elliptocytosis (oval )
   (b) autoimmune hemolytic anemias with a positive Coombs test

Iron deficiency anemia

Women are more likely than men to have anemia because of the loss of blood each month through menstruation. For them iron deficiency anemia is common.

In adults, iron deficiency anemia is most often due to chronic blood loss. This can be from menstruation or from small amounts of repeated bleeding (which can be very subtle) due, for instance, due to colon cancer.

Anemia can also be due to gastrointestinal bleeding caused by medications including such very common drugs as aspirin and ibuprofen. Acute blood loss from internal bleeding (as from a bleeding ulcer) or external bleeding (as from trauma) can produce anemia in an amazingly short span of time.

In infants and young children, iron deficiency anemia is most often due to a diet lacking iron.

Hereditary disorders can shorten the lifespan of the RBC and lead to anemia, as in sickle cell anemia. Hereditary disorders can also cause
anemia by impairing the production of hemoglobin, as in the alpha thalassemia and beta thalassemia.

Some physicians apparently give iron to all anemic patients whether they need it or not.

Other causes of anemia

Vitamin B12 is involved in pernicious anemia. Folate deficiency can be the culprit and be the basis of anemia. There can be rupture of red blood cells (hemolytic anemia) due to antibodies clinging to the surface of the red cells, as in hemolytic disease of the newborn and in many other conditions. A wide assortment of bone marrow diseases can cause anemia. For example, cancers that spread (metastasize) to the bone marrow, or cancers of the bone marrow (such as leukemia or multiple myeloma) can cause the bone marrow to inadequately produce red blood cells, resulting in anemia. Certain chemotherapy for cancers can also cause damage to the bone marrow and decrease red blood cell production, resulting in anemia. Finally, patients with kidney failure may lack the hormone necessary to stimulate normal red blood cell production by the bone marrow.

Pernicious anemia

Follow-up is important in pernicious anemia, since complications frequently develop. Many authors recommend that follow-up include endoscopy because of the increased risk of gastric cancer. Some recommend regular endoscopies so that cancer can be detected at an early stage. Others defer the procedure until symptoms appear or stool guaiac results are positive; however, at that point, the cancer may be unresectable.

The presence of a gastric carcinoid in the antral polyp will also be significant. In the past decade, it has been established that gastric carcinoid is an even more common complication of pernicious anemia than gastric cancer. The development of a carcinoid may result in part from hypertrophy of the enterochromaffin cells. Most gastric
carcinoids in patients with pernicious anemia have a benign course, but a small percentage metastasizes and produces a fatal outcome.

Immediate treatment with both B12 and folate is justifiable as long as the regimen is corrected as soon as blood test results identify the specific deficiency. The blood count will not begin to increase until after several days of vitamin therapy. If the hemoglobin level truly needs to be increased immediately, transfusion alone will suffice. Also, blood test results are equivocal on occasion. If the patient has not been treated, additional testing may resolve the uncertainty. But if the patient has already received vitamin therapy, the physician may be faced with a diagnostic dilemma. The high folate level is typical of B12 deficiency.

The physician may also order measurement of homocysteine and methylmalonic acid levels. Although serum levels of both often are misleadingly high in patients with renal insufficiency, they are sensitive markers of B12 deficiency.

However, homocysteine levels increase by similar amounts in patients with folate deficiency and other conditions. Measurement of the two metabolites is increasingly popular, since they can be useful in establishing the diagnosis when the clinical presentation or other laboratory results are equivocal. This is especially true in the early stages of vitamin B12 deficiency, when patients may have minimal or no anemia and borderline B12 levels.

Testing for the presence of anti-intrinsic factor antibody and elevated serum gastrin level can also be useful. Hemoglobin electrophoresis including hemoglobin A2 and hemoglobin F levels should also be checked.

It is axiomatic that a diagnosis of B12 deficiency indicates a gastrointestinal abnormality unless proven otherwise. The cause does not have to be established immediately, but it should be at some point. Many physicians do not consider this to be important, since treatment
and efficacy are the same regardless of whether the problem originates in the stomach or the intestine (i.e., inadequate gastric secretion of intrinsic factor or inadequate intestinal absorption of B12).

The difference does have potential repercussions, however. The gold standard for the diagnosis is the Schilling test—measurement of urinary excretion of radio-labeled oral B12. The test is inconvenient, however, because it requires a 24-hour urine collection. It also involves exposure to radioisotopes, albeit a very small exposure compared with that of many other tests. Unfortunately, few labs make the test and many hospitals do not do it. Fortunately, blood tests are available for detecting anti-intrinsic factor antibody and measuring the serum gastrin level. Together, the two tests permit diagnosis of pernicious anemia with 90% to 95% certainty. Pernicious anemia is neither synonymous with B12 deficiency nor its only cause, however. Other causes of B12 deficiency, such as sprue or bacterial overgrowth of the gut, each of which needs specific therapy, cannot be diagnosed by the two blood tests.

The most feared cause of macrocytic pancytopenia is aplastic anemia, which is characterized by low counts in all three blood cell lines. The cytopenia usually is quite severe.

Myelodysplastic syndromes are most common in the elderly and should be included in the differential diagnosis of elderly patients with pancytopenia, even if mild. Bone marrow aspiration and biopsy, with chromosome analysis, is required for diagnosis.

Pancytopenia can also result from trapping or pooling of cells in an enlarged spleen, as is often seen in patients with chronic liver disease.

Megaloblastic anemia is a common cause of macrocytic pancytopenia and by far the most readily treatable cause. Megaloblastic anemia can result from vitamin B12 or folate deficiency. Initially, patients have only a mild anemia with normal white cell and platelet counts. By the
time the anemia becomes severe, the white cell and platelet counts almost invariably are decreased.

Once megaloblastic anemia has been diagnosed, the next step is to determine whether it is caused by a deficiency of vitamin B12 or folate. Hence, the importance of a neurologic examination, an evaluation of mental function, and a dietary history cannot be over emphasized. The anemia can always be reversed by treatment, whereas neurologic abnormalities may or may not be.

In general, neurologic abnormalities do not occur in adult patients with folate deficiency (although they may result from coexisting conditions such as alcoholism). They do occur in about 50% of patients with vitamin B12 deficiency. Often the neurologic sequelae of B12 deficiency are more serious than the hematological abnormalities.

A high bilirubin level is an important clue to megaloblastic anemia. Pancytopenia in patients with megaloblastic anemia occurs because—even though bone marrow cell production is markedly increased—abnormal DNA synthesis causes precursor cells to die before they can be released into the blood stream. The red cell precursors have already produced hemoglobin, and after they die in the marrow and phagocytosis occurs, their heme is converted to bilirubin—just as in hemolytic anemia, in which the red cells are destroyed in the circulation.

It is true that in severe megaloblastic anemia, the MCV is usually elevated. When the hemoglobin level is 5.4 gm/dL, one might expect the MCV to be as high as 120 µm3.

For the sake of convenience, physicians often define macrocytosis as an MCV greater than 100 µm3. The actual threshold is closer to 97 µm3, however, and any reading above that should be considered suspicious. In fact, the ideal way to gauge the MCV is to compare it to the patient's usual value. If the patient customarily has an MCV of 85 µm3 and presents with an MCV of 92 µm3, the condition can be
regarded as macrocytosis, even though the reading is technically within the normal range. A final consideration in patients with macrocytosis is chronic alcoholism. Indeed, alcohol may be the most common cause of macrocytosis. Alcohol causes increased red cell size and often decreased platelet counts. However, except in the most severe cases, alcohol causes only mild anemia.

Many physicians would not consider a hemoglobin level of 11.3 gm/dL in a 70-year-old woman cause for concern. But she should have had a hemoglobin level higher than 12 gm/dL.

The key to the problem can be found in the CBC. A drop in the MCV is to be expected since treatment with vitamin B12 for curing the megaloblastic anemia. While many physicians regard an abnormally low MCV as any value below 80 µm³, the lower limit of normal is about 83 µm³.

The three most important conditions in the differential diagnosis of microcytic anemia are iron deficiency, anemia of chronic disease, and the thalassemic syndromes.

Diagnosing iron deficiency is important because it usually results from chronic blood loss. Its resolution takes precedence over its correction, especially when the anemia is mild.

Anemia of chronic disease is almost as common as iron deficiency anemia, and is similarly important as a clue to an underlying abnormality. Until proved otherwise, it indicates an inflammatory, infectious, or malignant process. It usually is not microcytic. In most cases, the MCV is in the low-normal range, although in about 15% of cases, it is slightly below normal.

*Anemias of Cancer*

There are two major causes of the anemia of cancer:

1. Chemotherapy, radiation therapy or surgery.
2. Anemias directly related to the cancer, which produces chemicals, such as cytokines, or anemias due to bone marrow infiltration by lymphomas or cancers. The anemia of cancers are affected by stimulation of the cellular immune system and inflammatory changes, which stimulate the production of chemicals called cytokines and affect both red cell production and survival. Several cytokines, including tumor necrosis factor (TNF), Interferon Gamma and Interleukin-1 (IL-1), can suppress bone marrow production (erythropoiesis) by affecting red cell production.

Approximately one-third of cancers have anemia, although, it is higher in lymphomas, genitourinary cancers and ovarian cancer - up to 50-60%. Hypoxia (low oxygen concentration) is associated with anemia, and this is regulated by erythropoietin production from the renal cortex. Erythropoietin is also produced in the liver under stress, and astrocytes in the brain can also produce some erythropoietin, which is protective against brain injury. In cancer-related anemias, there is also the shortening of the red cell life span, which is usually 120 days, to between 60 and 90 days.

The lifespan is also shortened in transfused red cells (hemolysis). Of note is that in anemia of cancer, there are similarities to the anemia of chronic diseases with a low serum iron and low transferrin saturation and normal or elevated ferritin level and a low reticulocyte count. The red cells are normochromic.

Thus, in summary, anemia of cancer is due to several causes:

1. A shortened red cell survival (hemolysis).
2. The activated immune system and macrophages, which produce cytokines, Interferon Gamma, IL-1 and tumor
necrosis factor, which can affect and impair iron utilization, suppress bone marrow production of red cells, as well as reduce erythropoietin production, which results in a decreased marrow stimulation for production of red cells.

Hypoxia (a decrease in oxygen concentration) stimulates erythropoietin production. There is a factor HIF-1 alfa and HIF-1 beta, which are hypoxia-inducible factors from hypoxic cells. Recent reviews have developed new concepts in the role of hypoxia, which can potentially increase angiogenesis and, thus, tumor growth.

*The Role of Anemia on Prognosis and Survival*

Blood is composed of cells that move around in a watery substance called plasma. The three basic types of cells in blood are red cells, white cells and platelets.

It works like this: your body uses oxygen to produce energy. The hemoglobin (Hb) in red blood cells carries oxygen to all parts of the body, providing the energy needed for normal activities and removes carbon dioxide. When you are anemic, less oxygen reaches your muscles and organs, like your heart. Not having enough red blood cells to carry oxygen places extra demands on your body.

Anemia can have a direct effect on prognosis and survival, and so, it may be very important to keep the hemoglobin at a higher level to decrease the effects of hypoxia, especially during treatment. There is a direct correlation between the hemoglobin level and the median P0₂ at the primary tumor site. There has also been a well-known effect of tissue hypoxia in radiation therapy and anemia relating to the efficacy of radiation therapy. This has been well-evaluated in head and neck cancers, and it has been shown that tissue hypoxia has a negative impact on local control and survival in cervical cancer as well. The radiation therapy damages DNA through its production of hydroxyl radicals. Thus, under hypoxic conditions, there is a smaller amount of oxygen available to produce DNA damage from free radicals, and so,
radiation therapy may be less effective. There seems to be a direct relationship between the hemoglobin increases during Epoetin alfa therapy and corresponding quality of life improvements in cancer patients receiving chemotherapy across the clinically-relevant range of 8-14 grams per deciliter. It was felt that maximal incremental gain in quality of life occurs when the hemoglobin range is 11-13 gm/dl.

_Physical Findings_

Iron deficiency is a common anemia worldwide, and in severe cases, there is spooning of the nails kylonychia, a smooth tongue and pallor of the skin.

In a physical examination, one needs to check for enlarged lymph nodes, which could reflect lymphoma, leukemia or an inflammation or infection, enlarged liver or spleen, which could reflect many different disease processes, and edema. There is often a murmur due to the decrease in red cells (hemoglobin), causing a flow sound on examination of the heart.

An examination of the peripheral blood smear is important, as in iron deficiency, it can show smaller red cells that have a poor hemoglobin concentration versus in hemolysis, larger cells that are often early cells called _reticulocytes_ - red cells that have lost their nuclei and have just entered the blood stream from the bone marrow. One also looks for fragmented cells or bizarre cell shapes (schiztocytes) that may often reflect hemolytic anemia and nucleated red cells, which are red cells that still have a nucleus. This reflects many different disease processes as an example of bone marrow distress or cancer involvement, hemolysis, bleeding or some hereditary anemias.

_Anemia and poor perinatal outcomes_

An association between moderate anemia and poor perinatal outcomes has been found through epidemiologic studies, although available evidence cannot establish this relation as causal. Anemia may not be a direct cause of poor pregnancy outcomes, except in the case of
maternal mortality resulting directly from severe anemia due to hypoxia and heart failure.

Preventing or treating anemia, whether moderate or severe, is desirable. Because iron deficiency is a common cause of maternal anemia, iron supplementation is a common practice to reduce the incidence of maternal anemia.

Another concern with iron supplementation in areas with endemic malaria is related to the possible interaction between better iron status and greater severity of malaria. A preponderance of studies have shown the greater rate of clinical malaria attack associated with iron supplementation. A more recent study, however, did not show that the risk of malaria justifies the withholding of iron. It is unlikely that withholding iron from individuals with significant iron deficiency will ever be an effective means of controlling malaria. The more appropriate approach for the areas with high endemic malaria is to provide malaria treatment or prophylaxis when iron supplementation is indicated.

Nevertheless, the effectiveness of large-scale supplementation programs needs to be improved operationally and, where multiple micronutrient deficiencies are common, supplementation beyond iron and folate can be considered.

The key argument supporting anemia as an outcome measure is related to the fact that red blood cells contain hemoglobin, which is an essential component of the respiratory system for oxygen transport. Any substantial reduction in red blood cells and hemoglobin reflects a reduced capacity of oxygen transport to tissue. Such a reduction in oxygen transport can be regarded as an adverse health outcome; thus, iron deficiency has a definite effect on health because of anemia (evidence of deficiency).

Defining the normal range of hemoglobin values

The hemoglobin cutoff value commonly used to define anemia is
based on the normality definition often applied to other clinical laboratory tests and in anthropometry.

For anemia, age- and sex-specific hemoglobin distributions are based on healthy reference samples (samples from persons with disease or nutritional deficiencies identified by other laboratory criteria are excluded). By convention, the central 95% of the reference hemoglobin distribution was considered the normal range. The 2.5th percentile hemoglobin value was the cutoff point for low hemoglobin or anemia. Conversely, the 97.5th percentile of the same distribution was the cutoff for high hemoglobin.

Because iron deficiency is often a major cause of anemia in many parts of the world, anemia screening is commonly used as a substitute for screening for iron deficiency.

However, the probability of iron deficiency in individuals who are anemic (positive predictive value) depends largely on the actual prevalence of iron deficiency in a specific population. Additionally, because many possible causes of anemia exist, such statistics-based anemia criteria provide only a guideline for establishing the probability of specific health and nutritional causes of anemia for a given population.

In essence, the hemoglobin-based definition does not provide sufficient information on the meaning of, or reason for, either anemia or high hemoglobin concentrations. Usually, the further a hemoglobin value is from the central tendency of the distribution, the greater the likelihood of finding pathologic reasons to explain the abnormal value.

Because of substantial normal variations in hemoglobin distribution across age, between sexes and races, and at different stages of pregnancy, the cutoff for low or high hemoglobin concentrations should be specific to sex and life cycle.

The use of inappropriate evaluative hemoglobin criteria during pregnancy can result in misinterpretation of the relation between
anemia and resulting health outcomes. An example of such misinterpretation is the disregard of normal hemoglobin concentration variations related to plasma volume changes during pregnancy, which can result in a striking association between preterm births and anemia.

**Physiologic significance of anemia**

Mild anemia is routinely defined as a hemoglobin value within 10 g/L of the anemia cutoff value. The World Health Organization recommends that severe anemia be defined as a hemoglobin concentration <70 g/L.

Hemoglobin concentrations below that of the mild anemia concentration and >70 g/L can be regarded as indicating moderate anemia.

Although oxygen carrying capacity is proportional to the circulating hemoglobin concentration, an individual with chronic anemia develops a compensatory mechanism to improve oxygen unloading to tissue from hemoglobin during the resting state.

This compensatory mechanism can maintain adequate tissue oxygen delivery down to a hemoglobin concentration of 70–80 g/L. In an exercise state, however, any loss of hemoglobin or red blood cell mass can be detected as loss in work capacity, even within a hemoglobin range of 120–130 g/L.

From a physiologic point of view, the evidence is clear that moderate anemia is undesirable, whatever the cause. If the cause of significant anemia is iron deficiency (evidence of deficiency), prevention and correction of iron deficiency anemia are indicated.

From the perspective of reproductive health outcomes, however, the evidence is not clear that anemia or iron deficiency is direct risk factors. Perhaps a concern more important than the health consequence of anemia is the cause of the anemia.
Some major causes of anemia have many other damaging effects or health consequences beyond anemia. For example, malaria is well known to cause severe anemia in many tropical areas, particularly among primigravidae, and it also contributes to the low birth weight of infants.

Sufficient evidence shows that moderate to very severe anemia can produce undesirable health consequences.

For nonpregnant women, this is equivalent to a hemoglobin concentration of 155–160 g/L. Analogous with mild anemia being within 10 g/L of the cutoff; a mild-high hemoglobin concentration would be 160–170 g/L.

For women, a hemoglobin concentration >170 g/L can perhaps be regarded as a moderately elevated value. During pregnancy, the upper level for defining high hemoglobin would be lower than that in nonpregnant women because of the physiologic changes in the hemoglobin concentration during pregnancy. Again, the meaning of the elevated hemoglobin concentration and the probability of association with adverse events depends on the specific individual or population under study.

Iron supplementation

A major factor that has limited the benefit of iron supplementation programs is the lack of clear evidence of an effective reduction in maternal anemia in field settings.

There are 2 aspects to this problem: one is related to the nature of the supplementation and the other is related to the operation of the program. In many developing countries, the principal reason that iron deficiency is common and can be severe is that diet quality is poor and
the intake of bioavailable iron is low, not necessarily that dietary iron intake is poor.

The best source of bioavailable iron is heme iron, which is found in animal muscle. Additionally, the absorption of nonheme iron can be affected by inhibitors or enhancers. In poor areas, the usual diet often consists mainly of unprocessed grain products that are relatively high in phytate, which is a known inhibitor of iron absorption.

Under conditions of poor diet quality, micronutrients other than iron are affected, including vitamin A, zinc, calcium, riboflavin, and vitamin B-12, and some of these micronutrient deficiencies also contribute to the severity of anemia.

Therefore, supplementation with iron (and folate) alone may not be effective in correcting nutritional anemia and may address only part of the problem concerning nutritional deficiencies. Consequently, where multiple nutrient deficiencies are common, a more appropriate micronutrient supplement formulation beyond iron and folate should be considered.

The commonly used iron and folate formulation is clearly suited for developed countries where the overall bioavailability of dietary iron is quite high and women at risk of iron deficiency anemia are often those with greater menstrual blood loss.

From an operational viewpoint, implementing iron supplementation programs is not an easy task because of the cost and multiple steps involved, including adequate communication with health workers and expectant mothers.

Evaluations of large-scale programs have found that the reduction of anemia is often limited because of a breakdown in the chain of events required to ensure proper functioning of programs. Perhaps the best argument against iron supplementation programs is the lack of effectiveness of these programs in controlling maternal anemia in some areas, not the lack of a medical indication for prevention of iron
deficiency and anemia. Better efforts to ensure program functioning appear to be a prudent alternative to abandoning programs.

To ensure the intended benefit of preventing significant iron deficiency anemia, efforts must be devoted toward improving the operation of supplementation programs and toward improving iron nutriture before pregnancy.

Combining other micronutrients with iron supplements is likely to increase the cost-effectiveness of programs because the same amount of effort will be exerted to provide not only iron, but other micronutrients as well. This may also increase the effectiveness of anemia control because other nutrient deficiencies can contribute to the burden of anemia.

Sufficient evidence exists to indicate that from a general health viewpoint, an iron-deficient state of nutriture can result in moderate and severe anemia, which is undesirable. Such evidence justifies efforts to prevent and treat significant iron deficiency, including iron supplementation during pregnancy when iron requirements are particularly difficult to meet.