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Iron Deficiency: Diagnosis and Treatment

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Mild iron deficiency is common among infants, adolescents and women during the childbearing years. Practical and economical approaches toward its identification, treatment and prevention are needed. Laboratory screening is based on hemoglobin or hematocrit determinations compared with age-specific and sex-specific reference standards. If blood specimens have been analyzed by electronic counter, the presence of a normal or low-normal value for red cell volume increases the likelihood that anemia is due to iron deficiency. Other laboratory tests that may be helpful in selected cases include determining serum ferritin, transferrin saturation or erythrocyte protoporphyrin values. However, in most cases, a simple therapeutic trial with ferrous sulfate may be instituted on the basis of history and a screening test alone. If repeat laboratory studies after a month show no improvement, iron treatment should be stopped and other causes of anemia should be considered.

IRON DEFICIENCY is the most commonly recognized nutritional deficiency in the United States and is by far the major cause of anemia. Most cases of iron deficiency anemia are mild, with hemoglobin concentrations no more than 2 grams per dl below the patient's potential hemoglobin value. Indeed, in many instances the hemoglobin concentration (or hematocrit) is within the low-normal range and is recognized as representing iron deficiency anemia only after the patient has had a substantial increase in these values in response to iron therapy.[1] Such overlap in values for normal and iron-responsive persons can often be resolved by the proper use of confirmatory laboratory tests or by an appropriate therapeutic trial.

Although the clinical manifestations are likely to be subtle, the identification of iron-deficiency is worthwhile for many reasons. There is growing evidence of decreased work performance in groups of iron-deficient subjects when anemia is mild. In addition, both in humans and in experimental animals, there are systemic abnormalities of behavior, immune function, intestinal absorption and thermogenesis that are related presumably to deficiences of essential tissue iron compounds.[2] In many instances, the diagnosis of iron deficiency also calls attention to a poor diet that should be corrected, to common causes of excessive blood loss such as menorrhagia or aspirin ingestion or to undiagnosed causes of occult in-

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ABBREVIATIONS USED IN TEXT

FEP = free erythrocyte protoporphyrin
MCH = mean corpuscular hemoglobin
MCHC = mean corpuscular hemoglobin concentration
MCV = mean corpuscular volume
TIBC = total iron-binding capacity

testinal bleeding. Therefore, it is useful to develop practical and economical approaches to the identification, treatment and prevention of this very common disorder.

Clinical Considerations

Because the clinical manifestations of iron deficiency are usually inapparent, most cases are detected by laboratory tests done at the time of a routine examination. High-risk groups, in whom such laboratory screening for iron deficiency has the highest yield, include infants, children, adolescents and women between the ages of menarche and menopause (Table 1).[3-5]

Among infants the prevalence of iron deficiency is highest between about 4 months when neonatal iron stores are first likely to be depleted and 3 years of age.[5] During this period, body iron should more than double, primarily to accommodate a rapid rate of growth and increase in red cell mass. Yet, the diet of infants and young children is often dominated by milk, which contains little iron and can also decrease the absorption of this mineral from other foods eaten at the same meal. Factors that are commonly associated with iron deficiency in infants include the ingestion of more than a quart of milk a day, which predisposes to occult intestinal blood loss in some infants. In infants whose rate of weight gain has been greater than average, iron deficiency is more likely to develop because of increased iron requirements. In premature infants and in twins, iron deficiency anemia may develop as early as three months after birth because neonatal iron stores are smaller and weight gain proportionately greater than in term infants.

Adolescents constitute another high-risk group.[5] Boys gain an average of 10 kg per year at the peak of their growth spurt. At about the same age as the growth spurt, and concurrent with sexual maturation, the concentration of hemoglobin increases between 0.5 and 1.0 grams per dl per year towards values that are characteristic of men.

TABLE 1.—*High-Risk Groups for the Development of Iron Deficiency*

Term infants between 6 months and 3 years of age and low birth weight infants as early as 3 months of age
Adolescents, particularly during the growth spurt
Women between menarche and menopause, particularly those who are pregnant or have a history of menorrhagia
Frequent blood donors
Chronic users of aspirin

These changes require an increase of about 25 percent in total body iron during the year of peak growth. The iron needs of adolescent girls are similarly large but are more evenly spread out over several years. The average weight gain at the peak of the growth spurt—9 kg per year—is almost as great as in boys; however, the concentration of hemoglobin changes very little during this time. The onset of menses, which usually occurs well after the adolescent growth spurt, requires additional iron to maintain a balance of this mineral in the system. Because the diets of teenagers are often poor sources of iron, mild iron deficiency is common during this period.

In women during the childbearing years, the major factors that predispose to iron deficiency anemia are menorrhagia and pregnancy.[3,4] Menorrhagia has been defined as blood loss exceeding 60 ml per menstrual cycle, and this has been reported to occur in about 19 percent of women who are using neither oral contraceptives nor intrauterine contraceptive devices (IUD's).[6] The use of IUD's increased the prevalence of menorrhagia substantially, to between 33 percent and 47 percent of women in one series, depending on the type of IUD.[7] Oral contraceptives, on the other hand, decreased menstrual blood loss by about half and were rarely associated with menorrhagia.

In women with menorrhagia, iron deficiency anemia is very likely to develop. The difficulty lies in identifying such women by their history because the estimation of menstrual blood loss is a highly subjective matter. Many women with subsequently documented menorrhagia, considered themselves to have either normal or scant menstrual bleeding. For this reason, laboratory screening for anemia is worthwhile at the time of a routine health examination in women, even when the history of menstrual blood loss is unimpressive.

Pregnancy is another period during which iron deficiency anemia is common. Iron requirements

TABLE 2.—*Stages in the Development of Iron Deficiency*

Stage 1: Depletion of Storage Iron	*Stage 2: Decrease in Transport Iron*	*Stage 3: Decreased Hemoglobin Production*
Low serum ferritin →		
	Low serum iron/TIBC →	
		High FEP
		Low MCV
		Low HGB

FEP = free erythrocyte protoporphyrin; HGB = hemoglobin; MCV = mean corpuscular volume; TIBC = total iron-binding capacity

increase to provide for an expanding blood volume and for the rapidly growing fetus and placenta.[3,4] Healthy women who are not pregnant have about 2.5 grams of total body iron of which an average of only 0.3 gram is storage iron. The iron needs during pregnancy average 1.0 gram and vastly exceed the amount of storage iron in most women; also, most of the iron must be supplied during the last half of pregnancy. Even with the normal adaptive increase in iron absorption that takes place during pregnancy, iron stores commonly become depleted and iron deficiency anemia develops. For this reason it is common practice to recommend iron or an iron-containing multivitamin-multimineral preparation during pregnancy. After delivery, iron requirements become more modest again because red cell mass decreases as the blood volume returns to baseline levels. Furthermore, the small amount of iron that is lost in breast feeding is roughly equivalent to the iron that is conserved by a decrease in menstrual blood loss during lactation.

The dietary history is particularly helpful in assessing risk of iron deficiency among children and in women after menopause. In these groups, iron balance is most precarious. Vegetarian diets are likely to provide very little iron that can be assimilated unless they are rich in vitamin C, which augments iron absorption. Less iron will also be available if plant or dairy products rather than meat are the major source of protein.

Normally, iron stores increase with age in men and women after menopause. In these groups, iron deficiency rarely develops on a nutritional basis alone.[3] Factors that can predispose to iron deficiency anemia in these groups, and even more so in the high-risk groups, are frequent blood donation (three or more times a year)[8] and aspirin ingestion (300 mg three times a day for a week, for example, has been reported to increase intestinal blood loss to 5 ml per day from a normal average of 0.5 ml per day).[9]

When there is no known basis for iron deficiency in men and in women after menopause, occult intestinal blood loss is a strong possibility and should be looked for. Often this is the first clue to the presence of intestinal abnormalities such as peptic ulcer, hiatal hernia, gastritis, polyps, regional enteritis, ulcerative colitis or carcinoma. In many developing countries, parasitic infestation, particularly with hookworn, is a very common cause of occult intestinal bleeding.[4] Schistosomiasis is also prevalent in several areas and can cause occult intestinal bleeding or urinary blood loss (which is usually apparent to the patient).

Laboratory Diagnosis of Iron Deficiency

The development of iron deficiency proceeds in a sequence of three overlapping stages (Table 2).[4,5] The first stage consists of a depletion of storage iron. This is most readily detected by determining the concentration of serum ferritin, which reflects the concentration of iron stores in the liver and bone marrow. An alternative is to obtain a bone marrow aspirate and stain it for iron to make a qualitative estimate of the amount present. Because of the greater simplicity of using blood specimens, the serum ferritin test is supplanting bone marrow aspiration for estimating amounts of storage iron. The second stage of iron deficiency consists of a decrease in transport iron. This is characterized by an increase in the iron-binding capacity in addition to a decrease in levels of serum iron. These changes are best reflected by determining transferrin saturation, which is calculated from the ratio of the other two values. The term latent iron deficiency is sometimes used to refer to these two preanemic stages of iron deficiency. The third stage occurs when the supply of transport iron decreases to the point of becoming a limiting factor that results in diminished hemoglobin production. This stage is characterized by an elevation of free erythrocyte protoporphyrin levels and the gradual development of detectable anemia and microcytosis. Iron therapy is usually directed at correction or prevention of the anemia and, in some cases, the clinical manifestations that characterize this stage.

Although it is convenient conceptually to classify laboratory tests according to these three stages of iron deficiency, laboratory results do not always conform strictly to this pattern among individual patients. For example, certain patients may prove to have an iron-responsive anemia despite a normal serum ferritin or transferrin

saturation determination. Such unexpected patterns of laboratory results may be a confounding factor, particularly in the diagnosis of mild iron deficiency.

The Use of Screening and Confirmatory Tests

The laboratory tests that are used in the diagnosis of iron deficiency can be conveniently grouped into screening tests and confirmatory tests. Screening tests are most commonly used in the initial evaluation of high-risk populations. The usual goal is to identify persons with anemia who are likely to have a hemoglobin response with administration of iron, an improved diet, or a combination of both. Alternatively, the screening of anemia may be done to detect occult disease in men or women after the menopause, in whom iron deficiency would not normally be expected to occur on a nutritional basis.

Among infants, laboratory testing to detect anemia is commonly recommended at about 1 year of age in term infants and 6 to 9 months of age in preterm infants, periods during which the prevalence of iron deficiency is highest in many populations.[10] Other suitable ages for the laboratory detection of anemia are between 2 and 3 years, at about 5 years in preschool children and in adolescence. The most appropriate times will differ according to the population. Nutritional iron deficiency is far more common among lower socioeconomic groups than in affluent populations.

Among women between the ages of menarche and menopause, laboratory screening for anemia is commonly done at the time of a regular physical examination and is particularly important when there is a history of menorrhagia. It is also an important part of prenatal care and should be done by the 20th week of pregnancy or earlier. In addition, screening for anemia is useful for those in the high-risk situations mentioned earlier (frequent blood donation and chronic use of aspirin). It is also part of the routine examination for prospective surgical patients and for many other patients who are admitted to hospital.

Screening Tests for Iron Deficiency

Hemoglobin and hematocrit. These are the most widely used tests to screen for anemia and iron deficiency. The concentration of hemoglobin is measured most reliably after accurate dilution of the blood specimen in a solution that converts hemoglobin to cyanmethemoglobin, which is quantitated spectrophotometrically. The analysis is then done either by a simple spectrophotometer (the type that is present in some physicians' offices) or as part of a complete blood count by a more elaborate electronic counter, typically found in a centralized laboratory. Blood counts obtained by electronic counter usually include red cell indices, which provide valuable additional information for the differential diagnosis of anemia, as will be discussed below. The electronic counter will also provide a calculated hematocrit; however, this determination is not considered as reliable a means of diagnosing anemia as is the hemoglobin concentration. In small office and clinic laboratories, the hematocrit is often measured by centrifugation of a minute amount of blood that has been collected in a heparinized capillary tube. The hematocrit is then calculated by comparing the height of the column of packed red cells with the height of the entire column of red cells and plasma. An advantage of this method is its technical simplicity, particularly when applied to finger stick capillary blood specimens. On the average, the hematocrit is roughly equivalent to the hemoglobin concentration multiplied by three.

With either the hemoglobin or hematocrit determination, it is essential to interpret the result in relation to age-specific and sex-specific reference standards.[5] Table 3 shows reference values for hemoglobin concentration after 6 months of age; laboratory testing for iron deficiency is rarely done before this age. The reference values for infants and children are based on the 95 percent range in venous blood from white, nonindigent

TABLE 3.—*Screening Tests for Iron Deficiency**

Age (year)	Hemoglobin (grams/dl)		Hematocrit (percent)		Mean Corpuscular Volume (fl)	
	Mean	Lower Limit	Mean	Lower Limit	Mean	Lower Limit
0.5-1.9	12.5	11.0	37	33	77	70
2-4	12.5	11.0	38	34	79	73
5-7	13.0	11.5	39	35	81	75
8-11	13.5	12.0	40	36	83	76
12-14						
Female	13.5	12.0	41	36	85	78
Male	14.0	12.5	43	37	84	77
15-17						
Female	14.0	12.0	41	36	87	79
Male	15.0	13.0	46	38	86	78
18-49						
Female	14.0	12.0	42	37	90	80
Male	16.0	14.0	47	40	90	80

*Estimated normal mean and lower limits of normal (mean minus 2 SD) for hemoglobin, hematocrit and mean corpuscular volume.

populations living at sea level and excludes those who have other laboratory evidence of iron deficiency or thalassemia minor.[11] In infants, the lower limit of the 95 percent range for hemoglobin is 11.0 grams per dl. After infancy, there is a gradual rise in hemoglobin values that continues throughout childhood. At puberty there is a further increase in concentration of hemoglobin in boys, and during adult life, the hemoglobin concentration in men is maintained at an average of about 2 grams per dl higher than in women. Data from population surveys show a slight, gradual decrease in hemoglobin concentration in elderly men.[12] It remains unresolved whether this is a normal concomitant of aging (possibly related to decreased androgen levels in elderly men) or, alternatively, whether it represents an increasing prevalence of anemia. For this reason, hemoglobin values for this group are not tabulated. In women, the hemoglobin concentration remains much more stable, and the lower limit of normal is considered to be 12 grams per dl from 8 years of age onward. An exception is during pregnancy, when the concentration of hemoglobin decreases concurrently with a great expansion in the blood volume. In pregnant women receiving iron supplements, the mean concentration of hemoglobin is lowest between about 18 and 30 weeks of gestation.[13] During this period, the lower limit of normal is approximately 10.5 grams per dl.

Mean corpuscular volume. Electronic counters have made the mean corpuscular volume (MCV) an accurate and practical laboratory test. Formerly, the determination of the MCV was a time-consuming and poorly reproducible procedure, because it was derived from the ratio of the hematocrit to the red cell count obtained by microscope. The electronic determination of red cell volume is highly reproducible and is actually less subject to sampling error than the hemoglobin determination because dilution by tissue fluid or fluctuations in plasma volume do not affect red cell size. When a blood count is obtained by electronic counter, it is important to give full attention to the result of the MCV because it provides valuable information to assist in the differential diagnosis. A low MCV with anemia favors the diagnosis of iron deficiency. It is also characteristic of thalassemia minor. However, most other anemias are characterized by normal or elevated MCV.

As in the case of hemoglobin and hematocrit determinations, red cell volume changes during development, making it important to refer to age-specific reference standards (Table 3).[11] Red cells are normally larger at birth than in adulthood, but red cell size decreases rapidly during the first six months of life. It is smallest during the remainder of infancy and gradually increases during childhood. There is little or no difference in red cell volume between sexes and values are relatively stable throughout adult life. However, there is some evidence that red cell size gradually increases with age and that the range in elderly persons is about 3 fl (μ^3) higher than in young adults.[14]

Other red cell indices obtained by electronic counter include mean corpuscular hemoglobin (MCH), which is derived by dividing the hemoglobin concentration by the red cell count and undergoes similar changes in iron deficiency as the MCV. The mean corpuscular hemoglobin concentration (MCHC) is the least directly measured and least useful of the indices obtained by electronic counter. Because the MCHC can be calculated by dividing hemoglobin by hematocrit, it is the only red cell index that is readily obtained without electronic counters. However, it is the least sensitive of the indices in the diagnosis of iron deficiency.[15]

Abnormal findings on screening tests. When the hemoglobin concentration (or the hematocrit) is below the lower limit of normal or in the low-normal range, there is a strong likelihood that an iron-responsive anemia exists. It is estimated that well over 50 percent of all anemic patients are iron deficient, and the percentage is probably much higher among women and children. If blood specimens have been analyzed by an electronic counter, the presence of a low or low-normal MCV in conjunction with anemia increases the likelihood that it is due to iron deficiency. When the presence of iron deficiency is suspected but not yet confirmed, there are several alternatives. When infants, children or women during the childbearing age have a mild anemia the odds are overwhelmingly in favor of iron deficiency for nutritional reasons, and a therapeutic trial with iron may be indicated. This argument can also be applied to those persons in whom anemia can be attributed to a specific cause of blood loss, as in frequent blood donors and chronic users of aspirin. The alternative is to select an additional laboratory study to strengthen the presumptive diagnosis of iron deficiency. The tests that are used most commonly to confirm this diagnosis are the free eryth-

TABLE 4.—*Confirmatory Tests for Iron Deficiency**

Serum ferritin <12 μg/liter
Transferrin saturation <16 percent
Free erythrocyte protoporphyrin >3 μg/gram hemoglobin (>100 μg/dl packed red cells)
Therapeutic trial of iron: 2-3 mg iron/kg/day *and* recheck screening test or tests after a month

*Alternatives after finding a low or borderline hemoglobin, hematocrit or MCV value (MCV = mean corpuscular volume).

rocyte protoporphyrin, serum ferritin, and transferrin saturation determinations. Each of these tests has certain advantages and disadvantages which will be discussed below.

Confirmatory Tests for Iron Deficiency

Serum ferritin. Ferritin is normally present in the serum but in such small quantities that it remained undetected until recently. It is measured by radioimmunoassay. An advantage of measuring the serum ferritin level is that it allows evaluation of iron status within the normal range, as well as in conditions of iron deficiency or excess—information that cannot be provided readily by other means. For example, the developmental changes in serum ferritin levels reflect known changes in iron stores within the normal range.[5] High values in newborn infants reflect abundant reserves that exist at this age. Values fall rapidly and remain low throughout infancy and childhood and in women of childbearing age; they rise in men and in women after menopause. At all ages, a serum ferritin value of less than 10 or 12 μg per liter (or ng per ml) indicates depletion of iron stores (Table 4).

A low concentration of serum ferritin is characteristic only of iron deficiency. However, values may be in the normal range despite the presence of iron deficiency, particularly in patients who have concurrent inflammatory disease.[17,18] Liver disease, even if it is mild, can result in major elevations of serum ferritin.[17] This is because serum ferritin has a very rapid turnover; studies using animals have shown that more than 90 percent of it is cleared by the hepatocytes. Consequently, the serum ferritin is of little use in diagnosing iron deficiency in patients who are suspected of having or who have been proved to have liver disease. However, serum ferritin determinations may be useful in diagnosing iron deficiency anemia in the presence of inflammatory diseases that do not affect the liver, if a lower limit of 25 or 50 μg per liter is used. For example, anemia in patients with rheumatoid arthritis cannot be assumed to be due to their chronic disease unless iron deficiency has been excluded as a contributing factor. Iron deficiency anemia due to blood loss is common among patients with rheumatoid arthritis who are chronic users of aspirin. A serum ferritin value of below 25 μg per liter in such persons makes it very likely that there will be a hemoglobin response to iron therapy.[18] However, a higher value is less helpful because it does not exclude the possibility of response.

In patients with chronic renal disease who are on hemodialysis regimens, blood loss is usually of sufficient magnitude as to make the development of iron deficiency inevitable. In such patients, serum ferritin determinations obtained at approximately three-month intervals will show a gradual decline in values.[19] When the serum ferritin concentration falls below about 50 μg per liter the initiation of iron prophylaxis is appropriate. However, when values are higher than 100 μg per liter, iron treatment is unnecessary and can be avoided.

Transferrin saturation. The transferrin saturation is calculated by dividing the concentration of serum iron by the total iron-binding capacity and multiplying by 100 to express the results as percent. Almost all of the iron in the serum is bound to the iron-binding protein transferrin. Serum iron and iron-binding capacity are generally measured by spectrophotometric techniques. The assay when done manually is time consuming and subject to errors due to contamination by iron in the environment. Automated techniques make it possible not only to obtain results more rapidly but to achieve greater reproducibility. The major disadvantage of the transferrin saturation test is the large biological variation that occurs in serum iron levels.[20] There is a pronounced diurnal variation in serum iron, usually with high values in the morning and low values at night. In a group of healthy adults the magnitude of this fluctuation was reported to fall from an average high of 47 percent in the morning to 13 percent at night, the latter value actually being below the normal range for adults.[21] It is therefore best to draw blood specimens for transferrin saturation testing in the morning or early afternoon because a low value is most likely to represent iron deficiency at this time of day. In adults, values of below 16 percent are considered indicative of iron deficiency. In infants and children the corresponding value is believed to be about 10 percent.[5]

Transferrin saturation may decrease in inflam-

TABLE 5.—*Dietary Measures to Improve Iron Absorption*

Include meat, fish, poultry and/or ascorbic-acid rich foods in meals
Avoid excessive amounts of tea and milk with meals
In infants, encourage breast-feeding but use iron-fortified formula in infants who are not breast-fed; use iron-fortified infant cereal when solid foods are introduced after 4 to 6 months of age

matory disease as well as in iron deficiency. In some instances the total iron-binding capacity (TIBC) is useful in distinguishing the two conditions. A TIBC of more than 400 μg per dl strongly suggests iron deficiency whereas a value below 200 μg per dl is characteristic of inflammatory disease. Unfortunately, the overlap of laboratory values between these two conditions is considerable, and most values will be in the intermediate range between 200 and 400 μg per dl.

Free erythrocyte protoporphyrin. The recent interest in the diagnostic use of this test is due to the development of a simple fluorescence assay and fluorometers that are designed for use in screening clinics. The latter require little technician time or training and make it practical to diagnose and initiate treatment for iron deficiency on a single patient visit. When insufficient iron is available to combine with protoporphyrin to form heme, there is an accumulation of protoporphyrin in red blood cells. The free erythrocyte protoporphyrin (FEP) can be measured rapidly by a simple fluorescence assay. This can be done either after a chemical extraction or directly on a thin film of blood, using an instrument specifically designed for this purpose. The FEP is elevated in both iron deficiency and lead poisoning,[16] and is therefore used to screen infants and young children in urban, low-income areas where both conditions are common. In such settings, the presence of an elevated FEP value requires further workup to determine whether lead toxicity or iron deficiency (or both) is responsible for the abnormality. The test is also useful in distinguishing iron deficiency from thalassemia minor; values are normal in thalassemia minor but elevated in iron deficiency.[22] However, because the erythrocyte protoporphyrin level is also elevated in inflammatory disease and lead poisoning, it is less helpful in distinguishing iron deficiency where the other two conditions are common.

Whether serum ferritin, transferrin saturation or the FEP is chosen as a confirmatory test often depends on local circumstances and the specific clinical situation. The local availability and relative costs of various tests will differ. The nature of the blood specimen is another factor. Capillary finger stick specimens are more suitable for routine blood counts (hemoglobin, hematocrit and red cell indices), serum ferritin and FEP than they are for transferrin saturation, which requires a larger blood specimen. It is also desirable to select tests that can provide a diagnosis and allow initiation of treatment on a single patient visit.

Management

Treatment of iron deficiency will involve dietary advice, a therapeutic course of iron or a combination of the two.

Diet. During the last decade it has been realized that there is a tremendous variability in iron absorption from different foods and that the extent to which iron can be absorbed is at least as important as the amount of iron in the diet.[23] In general, iron is poorly absorbed from vegetables, grain products, dairy products such as milk and cheese, and eggs. It is best absorbed from animal products such as meat, fish and poultry. When a variety of foods is eaten in a meal, certain individual foods can enhance or depress the absorption of iron from the entire meal. For example, the substitution of meat for milk, cheese or eggs as a protein source in a mixed meal has been shown to quadruple the aborption of iron from the entire meal.[24] The beverage taken with the meal can play a similarly important role. Compared with the use of water as a beverage, orange juice will double the absorption of iron from the entire meal, whereas the use of tea or milk decreases the absorption to less than half.[3,5,23] Such information lays the groundwork for making dietary recommendations to those with mild iron deficiency. Thus, inclusions of meat, orange juice and other ascorbic acid-rich foods in meals by such patients can be fostered, whereas milk or tea is best taken between meals and used in moderation by them (Table 5).

In infants, breast-feeding offers some protection against iron deficiency because breast milk iron is well absorbed even though present in very low concentration. When solid foods are introduced at 4 to 6 months of age, iron-fortified infant cereal is a good first choice; orange juice (or other ascorbic acid-rich juices) and meat are other suitable foods for subsequent inclusion in the diet. In infants who are not breast-fed, iron-

fortified formula is effective in preventing iron deficiency if started by 4 months of age in term infants and by 2 months of age in infants of low birth weight.[5,10]

In infants a pattern of consuming excessive amounts of milk while excluding other foods from the diet can be associated with iron deficiency[5] (excessive calcium interferes with iron absorption). In addition to treating such infants with iron, it is important to urge diversification of the diet and to limit the intake of milk to no more than about 750 ml per day.[10] When table foods or baby foods are provided in a meal it is useful to offer water or orange juice, or other ascorbic acid-containing juices, with that meal; milk need not be considered the only possible beverage for infants.

Therapeutic preparations of iron. The treatment of iron deficiency is relatively easy and inexpensive. The major problems are the poor compliance that is common with all prolonged courses of therapy and the frequency of gastrointestinal side effects.

In the vast majority of circumstances, oral iron therapy is most appropriate, and soluble ferrous iron salts are recommended because they are best absorbed.[3] Ferrous sulfate is cheapest and most widely used. An ample therapeutic dosage is 2 to 3 mg per kg of body weight per day. For adults, the most available form is the 300 mg capsule or tablet of ferrous sulfate, which contains 60 mg of elemental iron; liquid preparations are used particularly in treating infants and children and allow greater flexibility in dosage.

Absorption is greatest when iron is given between meals. If intestinal side effects are a problem, it is reasonable to decrease the dose. The percentage of iron absorbed is greatest with low doses; consequently, cutting the dose in half will result in assimilation of far more than half of the previously absorbed iron. Giving medication with meals will diminish the chance of side effects; however, it also decreases iron absorption by well over 50 percent. When iron is administered prophylactically or for mild iron deficiency, as during pregnancy, small doses of 1 mg per kg of body weight per day or less taken between meals are often adequate. Thus, a single daily dose of elemental iron of 30 to 60 mg per day is likely to achieve a good response, incurs little risk of gastrointestinal side effects and constitutes a simple enough regimen to favor good compliance.

Controlled release forms of iron. When there is a history or likelihood of gastrointestinal intolerance to iron (as during pregnancy) or if side effects persist despite reduction of dose and modification of dosage schedule, the use of controlled release forms of iron may be justified. Three types of preparation are in common use. In each of them ferrous sulfate is given in a form that is only gradually released during passage through the intestine. The first type is a capsule that contains numerous coated granules that dissolve at different rates in the intestine; the second consists of the iron salt packed in channels within a matrix of slowly soluble material, and the third is a tablet which gradually erodes in the intestinal tract. Some preparations of this type are absorbed as well as or perhaps slightly better than ferrous sulfate given in a rapidly soluble form.[25] With other preparations there is relatively little information about the extent to which they are absorbed.

Absorption during the course of therapy. The absorption of iron is by far the best during the first month or so of therapy when compliance is also likely to be best.[25] In one study, almost 15 percent of the administered dose (100 mg of elemental iron as ferrous sulfate at breakfast and dinner) was assimilated during the first week of therapy, yielding an average of 25 mg of iron absorbed per day. Between three and four weeks after beginning treatment, absorption had decreased by almost half, resulting in the assimilation of about 15 mg per day. After three to four months of therapy, iron absorption was drastically reduced to a mere 2 percent of the total dose, yielding an absorption of 4 mg per day. Because normal iron losses from the body are about 1 mg per day, the net increase in body iron at this stage of therapy was 3 mg per day, or about a tenth of what it was at the initiation of treatment. Similar experiments indicate substantially better absorption of iron when medication is taken between meals.

Optimally, iron therapy should be of sufficient duration to allow for complete restoration of the patient's ideal hemoglobin level as well as to provide some storage iron. This will generally involve treatment for three to six months. When the cause of iron deficiency cannot be corrected, as in patients with rheumatoid arthritis who require aspirin or in frequent blood donors (particularly women), long-term maintenance with iron in small doses is justified. There is little reason to give more than one tablet of ferrous sulfate (60

mg elemental iron) per day in these situations. Indeed, half this amount would be adequate.

Monitoring the results of a therapeutic trial. When iron treatment is instituted as a therapeutic trial, about two thirds of the hemoglobin deficit is corrected after a month, regardless of the initial severity of anemia. Therefore, a repeat of laboratory studies (the hemoglobin with or without the MCV) is conveniently done after one month of treatment. In patients with severe anemia, earlier evidence of response can be obtained by checking the reticulocyte count. There will be a significant elevation in reticulocyte count with peak values occurring between one and two weeks after initiation of treatment. However, when the anemia is mild, the reticulocyte count may not be significantly elevated on a single laboratory determination. It is therefore much more practical in such cases to rely on the correction of the hemoglobin concentration (with or without MCV) after a month.

If there has been no response after a month and medication has been taken regularly, other diagnoses must be considered. For example, thalassemia minor is relatively common among populations of Mediterranean, Asian or African origin, and it can also cause anemia and microcytosis. It is worth identifying thalassemia minor because affected patients are often given prolonged courses of iron treatment under the mistaken impression that they are iron deficient but relatively resistant to therapy. Another possibility is that occult blood loss during the period of treatment has been sufficient to negate any benefit of therapy. In such instances the reticulocyte count may be elevated and tests for occult intestinal blood loss are apt to be positive.

Avoid "shotgun" therapy. So-called hemantinics that contain iron, folate, vitamin B_{12} and other nutrients are *not* appropriate for a therapeutic trial. Although this therapeutic approach may temporarily reverse an anemia, it is likely to obscure an underlying disease that deserves attention. On the other hand, maintenance doses of micronutrients (equivalent to the recommended dietary allowances) in the form of multivitamin and multimineral preparations may be indicated to prevent deficiencies among certain high-risk groups (such as pregnant women and those adolescents who eat a particularly poor and erratic diet).

Failure of therapy when the diagnosis is well established. By far the most common cause of therapeutic failure is poor compliance. Lack of compliance may be due to forgetfulness, intestinal side effects or concern about either the stool turning dark or teeth becoming stained. The patient is often embarrassed about his failure to take medication and it may require skillful interviewing to bring out the correct history. Poor absorption of iron is relatively rare. If malabsorption of iron is suspected, however, a comparison between the concentration of serum iron before and two hours after a dose of 1 mg of elemental iron per kg of body weight as ferrous sulfate can be helpful.[26]

Parenteral iron. The use of intramuscular or intravenous iron therapy (generally in the form of iron dextran) is rarely warranted except when there is evidence of iron malabsorption, when the administration of oral iron medication cannot be relied upon, or when the possibility of follow-up is uncertain. Intramuscular injections may be painful and skin discoloration is common if special care is not taken to avoid back-flow into subcutaneous tissues. There is also concern that parenterally given iron may predispose to infection.[27] The basis for this concern has been derived primarily from in vitro studies, but some clinical studies are also suggestive. Severe anaphylactic reactions may occur with intramuscular or intravenous injections, but these are rare. Thus, parenteral medication should only be used when there is a reason to substitute it for orally given medication.

Conclusions

From one point of view iron deficiency is a gratifying condition to encounter. It is relatively easy to diagnose and treat, and it often provides the opportunity to improve a patient's diet or to detect occult disease. From another viewpoint, however, the high prevalence of iron deficiency represents a challenge in preventive medicine. Certainly, in infants and pregnant women who receive good health care, iron deficiency is unlikely to develop. But older children and women between the ages of menarche and menopause present a more complicated problem, because they are less likely to have periodic health examinations. For this reason, public health measures, such as iron fortification of cereal products, are important as an ancillary means of preventing iron deficiency. These efforts partially compensate for the decreasing iron content of the average diet.

The amount of iron available from foods has decreased with the increased use of refined foods and with the lower caloric intake that accompanies a more sedentary life-style. Iron deficiency represents a problem that can be alleviated by combining food fortification programs with appropriate medical care.

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