GUIDELINES FOR THE ASSESSMENT AND MANAGEMENT OF IRON DEFICIENCY IN WOMEN OF CHILDBEARING AGE

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EXECUTIVE SUMMARY

Maintenance of adequate iron stores in women of childbearing age is a health issue in the United States. This report provides guidelines developed by an ad hoc Expert Panel for the assessment and management of iron deficiency in women during the reproductive years. It was prepared in response to a request from the Center for Food Safety and Applied Nutrition (CFSAN) of the Food and Drug Administration (FDA), which is responsible for establishing and maintaining policies regarding food fortification and for ensuring safe use of nutrient supplements.

The prevalence of iron deficiency in the total U.S. population is sufficiently low to preclude consideration of increasing current levels of iron fortification in standardized foods; however, because of iron losses of menses and pregnancy, the prevalence of iron deficiency remains relatively high in women of childbearing age. Iron deficiency develops in this subgroup despite fortification of foods with iron at levels that are adequate to prevent iron deficiency in most of the population and use of nonprescription nutritional supplements containing iron by approximately 25 percent of women 18 through 44 years of age. The prevalence of iron deficiency (about 10 percent) in adolescent and adult females in the U.S. does not justify a recommendation for iron supplementation of all women of childbearing age. Selective intervention targeted for women with iron deficiency is an alternative means of improving iron status in this subgroup. This report provides guidelines for this purpose.

PHYSIOLOGICAL AND SOCIODEMOGRAPHIC RISK FACTORS FOR IRON DEFICIENCY

Blood loss (menstrual and gastrointestinal losses, and blood donation) represents a major route of iron depletion for nonpregnant women. Pregnancy, especially pregnancy during early adolescence or repeated and closely spaced pregnancies, creates a high demand for iron that is not readily met by dietary iron. Sociodemographic risk factors for iron deficiency are poverty, lower education level (less than a high school education), higher parity (three or more children), and black and Mexican American backgrounds.

Because iron requirements are relatively high in relation to energy needs, some women may consume diets that contain inadequate amounts of bioavailable iron. Overall, average intake of iron (10 mg/day) is associated with adequate iron status in at least 86 percent of women of childbearing age. Although this suggests that dietary iron consumption may be sufficient for most women, black women, those living below poverty, and those with less education tend to have somewhat lower mean iron intakes. In all sociodemographic subgroups, women who have larger blood losses, those who usually consume low-calorie diets, and those who follow strict vegetarian diets may have difficulty consuming sufficient dietary iron to meet their needs.

DETECTION OF IRON DEFICIENCY ANEMIA IN HEALTHY NONPREGNANT WOMEN OF CHILDBEARING AGE

The Expert Panel considered detection of iron deficiency anemia the most important priority in healthy, nonpregnant women. Iron treatment of nonpregnant women should be used primarily to prevent the adverse physiological consequences associated with iron deficiency anemia.
The Expert Panel recommended a two-step approach to screen for the presence of anemia and to make an etiologic diagnosis of iron deficiency in women of childbearing age. Screening for anemia should be done for all apparently healthy women without clinical evidence of anemia at general health maintenance visits. Making an etiologic diagnosis in women who tested positive during screening applies only to healthy women. The approach applies only to the detection, treatment, and follow-up of anemia caused by uncomplicated iron deficiency in healthy women whose evaluation includes appropriate history and physical examination. The Panel recommendations do not provide a scheme for the differential diagnosis or management of other causes of anemia.

Screening for anemia

Measurement of hemoglobin concentration was recommended as the screening tool for iron deficiency anemia. Hemoglobin concentration < 12 g/dL (120 g/L) was considered the most appropriate cutoff to designate anemia in women of childbearing age. Adjustments for higher altitudes and smoking were given.

Women with unadjusted hemoglobin concentrations between 10.0 and 12.0 g/dL (100 and 120 g/L) were targeted as the group who would benefit from iron therapy. Hemoglobin concentration in this range is likely to be caused by uncomplicated iron deficiency. Hemoglobin concentration < 10.0 g/dL (100 g/L) is more likely to have an additional cause such as chronic disease or blood loss and should always prompt a thorough investigation to determine its cause.

Because of the greater variability of capillary blood samples, hemoglobin measurements should be made on venous blood samples whenever possible. A low hemoglobin value obtained on a capillary sample should be confirmed on a venous sample before a diagnosis of anemia is made.

Measurement of hematocrit is an alternative screening tool for anemia. However, hematocrit determinations are subject to more sources of error than hemoglobin assays. When hematocrits are used for screening, the cutoff value indicative of anemia in women is 36 percent. Additive adjustments to hematocrit for altitude and smoking were given.

Etiologic diagnosis of iron deficiency

Measurement of serum ferritin concentration was viewed by the Expert Panel as the best overall single test for etiologic diagnosis of iron deficiency in a preselected population of anemic women because of its direct proportionality to total iron stores. Its relative stability with repeated measurements in the same individual also makes it a useful test to monitor iron repletion during treatment.

Serum ferritin concentrations below 12 µg/L in adults are considered to represent total depletion of iron stores and are unquestionably diagnostic of iron deficiency. To confirm the presence of iron deficiency in women already identified as anemic by their low hemoglobin concentrations, a cutoff of less than 20 µg/L was considered a more appropriate value. Raising the cutoff value for serum ferritin increases the sensitivity (positive results in diseased persons) of the screening procedure at the expense of selectivity (negative results in healthy persons). The prevalence of depleted iron stores will be increased in the preselected population receiving the ferritin test. Therefore, the predictive value of the serum ferritin is increased.

Alternatives to the measurement of serum ferritin concentration are a therapeutic trial of oral iron or additional laboratory tests (transferrin saturation or erythrocyte protoporphyrin). The therapeutic trial consists of determining whether there is a rise in hemoglobin concentration after 6 weeks of administering a therapeutic dose of iron (120 mg/day). A small prevalence of false positive
results in the presence of concurrent inflammation complicates the interpretation of a positive result in the transferrin saturation or erythrocyte protoporphyrin tests. An alternative for possible future use is the serum transferrin receptor assay which may provide a more sensitive means of detecting iron deficiency than currently available assays.

TREATMENT AND FOLLOW-UP OF UNCOMPLICATED IRON DEFICIENCY ANEMIA IN NONPREGNANT WOMEN

The objectives of treating women with iron deficiency anemia are twofold: (1) to reverse the anemia, as measured by the return of hemoglobin concentration to normal levels [12 g/dL (120 g/L)] and (2) to build iron stores to protect against the recurrence of anemia. Because serum ferritin levels parallel total body iron stores, replenishment of iron stores is evaluated best by measurement of the serum ferritin concentration.

The recommended strategy for reversing uncomplicated iron deficiency anemia is oral administration of a well-absorbed soluble ferrous iron compound with a defined follow-up schedule and dietary counseling. Although iron deficiency is the major iron status concern in women of childbearing age, some concern about possible effects of excess iron is also appropriate. Accordingly, iron supplements should not be given unnecessarily.

Treatment

The Expert Panel recommended a two-part treatment strategy: (1) initiation of therapy with a relatively large quantity of iron to reverse the anemia over a timespan of 6 weeks to 6 months, and (2) once the anemia is corrected, maintenance with a smaller quantity of iron to build stores and prevent recurrence of the anemia. The total timespan for therapy and maintenance should not exceed one year unless the ferritin concentration remains below 20 μg/L.

- For therapy, the total daily dose should be 120 mg but can range from 60 to 180 mg. Iron should be taken in divided doses two or three times per day. Each dose should contain no more than 60 mg iron.

- For maintenance, the total daily dose should be 30 mg but can range from 15 to 60 mg.

- Use of all oral iron preparations should be medically supervised.

- To maximize absorption, iron compounds should be taken alone, not as part of a multivitamin and mineral preparation or with other mineral supplements.

- To maximize absorption, iron should be taken with liquids such as water or fruit juice between meals or at bedtime. Beverages that inhibit absorption of supplemental iron (coffee, tea, or milk) should not be consumed at the time the iron is taken.

- Dietary counseling should provide patient education about forms, sources, and relative absorption of dietary iron. Effects of enhancers (ascorbic acid and meat, fish, and poultry) and inhibitors of nonheme iron absorption (e.g., coffee and tea and some calcium supplements) should also be stressed.
Follow-up

Both the therapeutic and maintenance phases of oral iron treatment should be followed up and maintenance should not be extended indefinitely. Response to oral iron should be evaluated at 6 weeks and 6 months after initiation of therapy.

- **After 6 weeks** of oral iron therapy, the venous hemoglobin concentration should be measured in all patients.
  - If the hemoglobin concentration is >12 g/dL (120 g/L), reduction of oral iron to a maintenance dose (30 mg/day, range 15 to 60 mg) can be considered as early as 6 weeks. The continued presence of risk factors should be considered in deciding whether to extend the therapeutic dose for a longer time.
  - If the hemoglobin concentration has risen but has not yet reached 12 g/dL (120 g/L), the therapeutic dose should be continued.
  - If the hemoglobin concentration has not risen and patient compliance has been poor, a change in the iron compound or a lower therapeutic dose and additional counseling may be indicated. The hemoglobin concentration should be reevaluated at 12 weeks.
  - If the hemoglobin concentration has not risen and patient compliance has not been a problem, reevaluate the etiology for causes other than uncomplicated iron deficiency.

- **After 6 months** of oral iron treatment, the serum ferritin concentration should be measured.
  - If the serum ferritin concentration is >40 μg/L, oral iron treatment should be discontinued.
  - If the ferritin concentration is 20 to 40 μg/L, continued administration of maintenance levels of oral iron should be considered in terms of the continued presence of risk factors or underlying causes. For example, anemia resulting from heavy menstrual losses or regular blood donation is more likely to recur than anemia resulting from multiple pregnancies. Iron status should be evaluated again at 12 months.
  - If the ferritin concentration is <20 μg/L, the maintenance dosage of oral iron should be continued. Iron status should be evaluated again at 12 months.

Indications to discontinue oral iron treatment include the reversal of anemia if no critical risk factors are present, replenishment of iron stores, or the onset of menopause. After menopause, iron needs are decreased and pregnancy and menstruation no longer protect against manifestations of hereditary iron–storage diseases.

Results of experimental and clinical investigations on the use of oral iron preparations at the recommended therapeutic and maintenance doses, maximizing absorption of oral iron preparations and dietary iron, and the expected time course of response to treatment were summarized.
USE OF ORAL IRON PREPARATIONS DURING PREGNANCY

Women with a greater likelihood of depleted iron stores prior to pregnancy (younger adolescents, regular blood donors, and women with large menstrual losses) are at higher risk for development of iron deficiency anemia during pregnancy. Likewise, women with sociodemographic risk factors (poverty, lower education level, higher parity, and black or Mexican American backgrounds) are likely to be at greater risk for development of anemia during pregnancy.

Because of the increased likelihood of iron deficiency during pregnancy, the Expert Panel recommended daily use of oral iron supplements containing 30 mg of ferrous iron by all pregnant women during the second and third trimesters. Guidance concerning the importance of dietary iron during pregnancy should also be a part of prenatal care for all pregnant women.

Because concentrations of hemoglobin and serum ferritin normally change over the course of pregnancy, different criteria are needed for the diagnosis of anemia in pregnant women. Hemoglobin levels of 11.0, 10.5, and 11.0 g/dL (110, 105, and 110 g/L) are considered the cutoff values for anemia in the first, second and third trimesters, respectively. Equivalent cutoff values for hematocrit are 33.0, 32.0, and 33.0 percent, respectively. If there is evidence of iron deficiency anemia at any time during pregnancy (low hemoglobin or hematocrit plus a serum ferritin concentration below 20 µg/L), a therapeutic dose of ferrous iron (60 to 120 mg iron/day with no more than 60 mg for any dose) should be given between meals or at bedtime to correct the anemia. This level of iron treatment should be continued until the hemoglobin concentration is within normal limits for the stage of pregnancy. At that time, the dose can be reduced to a maintenance level of 30 mg/day.
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I. INTRODUCTION

A. BACKGROUND

Iron deficiency is probably the most widespread deficiency of a single nutrient in the U.S. population and is considered the most common cause of nutritional anemia in humans (Hillman and Finch, 1988; U.S. Department of Health and Human Services and U.S. Department of Agriculture, 1986). For some segments of the U.S. population, such as men and postmenopausal women, the prevalence of iron deficiency is quite low. However, for some other subgroups, a higher prevalence of iron deficiency remains a public health concern (Life Sciences Research Office, 1989).

Data from the second National Health and Nutrition Examination Survey (NHANES II) and the Hispanic Health and Nutrition Examination Survey (HHANES) indicate that young children, adolescents, and women of childbearing age are subgroups at greatest risk of iron deficiency (Life Sciences Research Office, 1989; Looker et al., 1989; Pilch and Senti, 1984). This report focuses on women who appear to be at increased risk of iron deficiency throughout the reproductive years (Looker et al., 1989; Pilch and Senti, 1984) because of iron losses of menses and pregnancy. Iron deficiency occurs in women of childbearing age despite fortification of foods with iron at levels that are adequate to prevent iron deficiency in most of the population (Yetley and Glinsman, 1983) and use of nonprescription nutritional supplements containing iron by approximately 25 percent of women 18 through 44 years of age (Moss et al., 1989).

The prevalence of iron deficiency in the total U.S. population is sufficiently low to preclude consideration of increasing current levels of iron fortification in standardized foods (Food and Drug Administration, 1978; Yetley and Glinsmann, 1983); however, additional evaluation is needed to identify approaches to detect and manage iron deficiency in women of childbearing age. The prevalence of iron deficiency (about 10 percent) in adolescent and adult women in the United States does not justify a recommendation for iron supplementation of all women of childbearing age. Selective intervention targeted for these women is an alternative means of improving iron status in this subgroup.

The Food and Drug Administration (FDA) perceives the assurance of adequate iron stores during the childbearing years as a health issue for women. As part of its mandate to ensure the safety and adequacy of the food supply and to provide nutrition information to the public, the Center for Food Safety and Applied Nutrition (CFSAN) of FDA is responsible for establishing and maintaining policies concerning food fortification and for ensuring safe use of nutrient supplements. Therefore, CFSAN requested that the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) undertake a study to evaluate current knowledge and provide guidance to FDA on the assessment and management of iron deficiency in women during the childbearing years.

B. SCOPE OF WORK

The Scope of Work for the study specified guidance on the following:

- criteria for identifying individuals at risk of iron deficiency;
- diagnostic techniques for assessing iron status;
- appropriate tests for detecting anemia caused by iron deficiency; and,
strategies for management of anemia resulting from iron deficiency including recommended
duration of therapy, follow-up during therapy, and indications for discontinuing therapy.

To perform this study, LSRO convened an ad hoc Expert Panel of scientists with expertise in
disciplines related to clinical detection and management of iron deficiency. These scientists are
identified in Chapter IX.

As a consultative group to LSRO, the ad hoc Expert Panel developed guidelines for detection,
treatment, and follow-up of iron deficiency anemia in women of childbearing age at the level of the
primary health care provider. In making these recommendations, the Expert Panel recognized that
implementation of these guidelines may not be feasible immediately in all types of health care
settings.

In discussions leading to development of this LSRO report, the Expert Panel used as a model the
concept that iron deficiency develops as a continuum beginning with depletion of iron stores and
progressing to the development of a typically microcytic, hypochromic anemia. Particular
physiological and sociodemographic factors that increase the likelihood that individual women will
develop iron deficiency and anemia during their reproductive years were identified. A two-step
approach for screening and etiologic diagnosis of iron deficiency anemia was recommended as a part
of general health maintenance examinations. Recommendations for treatment with oral iron and
dietary counseling were made together with recommended strategies for follow-up of individuals
receiving oral iron treatment.
II. IRON STATUS CONCERNS IN WOMEN OF CHILDBEARING AGE

In healthy individuals, iron status is determined by the balance between intestinal absorption of ingested iron and losses (Finch and Huebers, 1987). Iron balance may be disturbed by excessive losses or excessive accumulation of iron. For women of reproductive age, large iron losses (heavy menstrual losses and increased demand for iron during pregnancy) cannot always be compensated by increased absorption and iron depletion may occur. Because of these relatively large iron losses, excessive iron accumulation is unlikely in women during the childbearing years. Although development of iron deficiency is the major health concern in these women, toxic effects of excess iron must be recognized as a possible, although unlikely, adverse health effect.

A. IRON DEPLETION

Iron depletion is often depicted as developing in three discrete stages of increasing severity (Bothwell et al., 1979). The description of these stages aids in discussing iron nutriture and in classifying different degrees of iron depletion. Changes in body iron compartments and measures of iron status during iron depletion are illustrated in Figure 1.

During the first stage of iron depletion, iron stored in liver, reticuloendothelial cells, and red blood cell precursors in bone marrow is decreased by inadequate intake of dietary iron, by excessive losses, or a combination of both. Total storage iron can vary greatly in healthy persons and the presence of low stores may be the usual physiological state for many menstruating women. Although low iron stores are not associated with adverse biological consequences, their presence represents a state of increased vulnerability for developing more severe iron deficiency. Decreases in storage iron elicit a homeostatic response through increased gastrointestinal iron absorption. Consequently, relatively few women of childbearing age who have depleted iron stores actually progress to frank iron deficiency anemia (Bothwell et al., 1979; Dallman, 1986).

Depletion of iron stores is most readily detected by a decline in serum ferritin concentration. Serum ferritin levels are related somewhat quantitatively to body iron stores. In the concentration range of 20 to 300 μg/L, each μg/L serum ferritin represents about 10 mg storage iron in adults (Cook and Skikne, 1982). Inflammation and infection increase serum ferritin levels and depleted iron stores may be masked by these conditions.

During the second stage of depletion (iron deficiency without anemia), iron stores are reduced to such an extent that the supply of iron limits the rate of hemoglobin synthesis. The possibility of adverse physiological effects first exists with this degree of iron depletion which may be considered to represent early or mild iron deficiency. Although hemoglobin concentration decreases at this stage, the decline is not sufficient to meet the laboratory criteria of anemia. As shown in Figure 1, this degree of iron depletion is characterized by a rise in the concentration of erythrocyte protoporphyrin (an intermediate in hemoglobin synthesis) and a decrease in transferrin saturation (serum iron/total iron-binding capacity). Infection and inflammation and chronic disease produce these same changes in erythrocyte protoporphyrin concentration and transferrin saturation. Lead poisoning also increases erythrocyte protoporphyrin levels.

During the third stage of iron depletion, the limited iron supply reduces hemoglobin synthesis sufficiently to result in frank iron deficiency anemia. In addition to the changes in ferritin and erythrocyte protoporphyrin concentrations and transferrin saturation, hemoglobin concentration falls below 12 g/dL (120 g/L), the threshold level for anemia in women (Bothwell et al., 1979). Mean
Figure 1. Changes in body iron compartments and measures of iron status during iron depletion (modified from International Nutritional Anemia Consultative Group, 1977).
corpuscular volume (MCV) is usually decreased also. Decreased exercise tolerance and work performance are physiological consequences of frank iron deficiency anemia in women (Cook and Lynch, 1986; Dallman, 1982).

In this report, the term "iron deficiency" is applied to the second and third stages of iron depletion.

B. IRON EXCESS

Iron overload can develop as a result of excessive iron absorption from the intestinal tract or administration of multiple transfusions for some types of anemias. Increased iron absorption occurs as a result of hereditary hemochromatosis, a genetic disorder that results in iron overload. The frequency of occurrence of homozygous hereditary hemochromatosis is 3 to 8 per thousand (Edwards et al., 1988; Krikker, 1988). Symptomatic hemochromatosis is much less common among homozygous females than among males, in part because of iron losses by women during menstruation and pregnancy. Although the iron losses of menstruation and pregnancy diminish the risk of developing clinical manifestations in women homozygous for hereditary hemochromatosis, the relative protection provided by these increased iron losses is lost at menopause.

C. OTHER POTENTIAL CONCERNS

In recent years associations between higher levels of some indicators of iron status and increased risk of some types of cancer have been reported in epidemiological studies of several populations in the United States (Freudenheim et al., 1990; Friedman and Ury, 1980; Selby and Friedman, 1988; Stevens et al., 1988). Types of tumors reported have not shown a consistent pattern among studies and design flaws resulting in inadequate control of confounding factors have complicated interpretation of these studies. In the instances in which further investigations have been carried out, they have not confirmed the findings of the first studies (Selby and Friedman, 1988; Yip et al., 1991).

Although a role for iron in carcinogenesis is biologically plausible and data from some of the epidemiological studies cited above have implied a possible association between iron status and incidence of cancer, the available evidence does not suggest that increased body stores are a risk factor for cancer. Nonetheless, some concern about toxic effects of iron excess is appropriate. Accordingly, iron supplements should not be given unnecessarily.
III. PREVALENCE OF IRON DEFICIENCY IN WOMEN OF CHILDBEARING AGE

A. NONPREGNANT WOMEN


In NHANES II, low hemoglobin concentration denoting anemia (<12 g/dL or 120 g/L), was present in about 10 percent of women 11 through 44 years of age (Pilch and Senti, 1984). However, anemia is not always due to iron deficiency. Because no single biochemical or hematological indicator is considered diagnostic for iron deficiency with or without anemia, an Expert Scientific Working Group developed ferritin and MCV models based on the presence of abnormal values for two or more iron status indicators (Pilch and Senti, 1984). The use of multiple tests in parallel for diagnosis is employed widely in many aspects of clinical medicine.

Estimates of prevalence of iron deficiency for all races, with or without concurrent anemia, in nonpregnant females 11 through 44 years of age are shown in Table 1. Estimates of prevalence for the two models vary because the ferritin model may detect a milder degree of iron depletion than the MCV model. The presence of inflammation may increase prevalence estimates made using these two models because transferrin saturation and erythrocyte protoporphyrin concentration are similarly affected by iron deficiency and inflammation. Prevalence estimates made by other methods and restricted to a subsample of the NHANES II population with ferritin measurements (Cook et al., 1986) were in accord with the estimates of Pilch and Senti (1984).

Table 1. Prevalence of Iron Deficiency in Nonpregnant Females, Estimated by Means of Two Models: NHANES II, 1976–80.¹

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Ferritin Model² (percent)</th>
<th>MCV Model³ (percent)</th>
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<tr>
<td>11–14</td>
<td>6.1</td>
<td>3.4</td>
</tr>
<tr>
<td>15–19</td>
<td>14.2</td>
<td>4.9</td>
</tr>
<tr>
<td>20–44</td>
<td>9.6</td>
<td>5.4</td>
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¹ Modified from Pilch and Senti (1984).

² Requires abnormal values for at least two of the three following indicators: ferritin (<12 µg/L), transferrin saturation (<16%), and erythrocyte protoporphyrin (>70 µg/dL).

³ Requires abnormal values for at least two of the three following indicators: transferrin saturation (<16%), erythrocyte protoporphyrin (>70 µg/dL), and MCV (<80 fl).

Univariate analyses for effects of sociodemographic factors on prevalence of iron deficiency indicated that iron deficiency was higher in black women, and in women living in poverty, with less education, and with three or more children. Multivariate analyses to control for confounding among these variables were not done (Pilch and Senti, 1984).
The prevalence of iron deficiency (MCV model) in nonpregnant women from three Hispanic groups (Mexican Americans, Cubans, and Puerto Ricans) has been compared with that of non-Hispanic white and non-Hispanic black women (Looker et al., 1989). Prevalences did not differ statistically among the three Hispanic groups but prevalence was higher \((p<0.05)\) in Mexican American women 20 to 44 years of age than in non-Hispanic white or non-Hispanic black women. This difference was attributed, at least in part, to higher parity among Mexican-American women (Life Sciences Research Office, 1989).

B. PREGNANT WOMEN

The small numbers of pregnant subjects in the NHANES I and II and HHANES samples do not permit reliable estimates of the prevalence of iron deficiency in a nationally representative sample of pregnant women in the United States. However, hemoglobin/hematocrit data from the 1987 CDC Pregnancy Nutrition Surveillance System (Preg NSS) indicate that prevalence of anemia in low-income high-risk pregnant women increases during the second and third trimesters. Prevalences for white and black women were 3.5 percent and 12.7 percent respectively during the first trimester, 6.4 and 17.8 percent in the second trimester, and 18.8 and 38.1 percent in the third trimester. Prevalences were also generally higher among younger women (Centers for Disease Control, 1990). In addition, several studies document the occurrence of anemia in pregnant women in western European countries and suggest that iron supplementation is needed to prevent this occurrence (Puolakka et al., 1980; Svanberg et al., 1975a; Taylor et al., 1982).
IV. RISK FACTORS FOR DEVELOPMENT OF IRON DEFICIENCY

A. PHYSIOLOGICAL FACTORS

Iron is metabolized by very efficient and tightly regulated physiological mechanisms. More than 90 percent of iron released from catabolism of hemoglobin is conserved and used again. The capacity of the intestinal mucosa to absorb iron is inversely related to iron stores (Charlton and Bothwell, 1983). The amount of iron absorbed by men and postmenopausal women must balance only the basal losses resulting from desquamation of intestine and skin cells, about 1 mg/day (Bothwell et al., 1979). However, for women of childbearing age, other factors substantially increase the amount of iron required to maintain iron balance (Fairbanks and Beutler, 1988). These include blood loss and pregnancy, especially repeated and closely spaced pregnancies. Consuming sufficient dietary iron without consuming energy in excess of needs may be difficult for some women with higher iron losses.

1. Blood loss
   a. Menstrual losses

Menstruation represents a major loss of iron for nonpregnant women during the childbearing years. Mean menstrual blood loss in healthy women with normal menstruation was found to be about 33 ml per month, but the distribution suggests that a relatively small percentage of women have substantially higher losses. The 95th percentile of blood loss was about 76 ml per month, more than twice as high as the mean (Cole et al., 1971; Hallberg et al., 1966). If a hemoglobin concentration of 12 g/dL (120 g/L) is assumed, about 14 and 31 mg of iron would be lost in menses every month by women at the mean and 95th percentile, respectively. Although women with average menstrual losses require about 1.5 mg/day of iron to maintain iron balance (1 mg/day to replace basal losses and 0.5 mg/day to replace menstrual losses), those with losses at the 95th percentile require about 2.1 mg/day of iron.

Menstrual losses of individual women change little from month to month, but considerable variation occurs among individuals (Hallberg et al., 1966). Thus, larger blood losses occur consistently in some women, predisposing them to the development of anemia. The proportion of women with anemia (hemoglobin concentration <12 g/dL) increased substantially as menstrual losses increased beyond 60 ml (Hallberg et al., 1966).

The onset of menstruation soon after a period of rapid growth results in a high demand for iron during early adolescence. On the average, menarche occurs about one year after the peak growth spurt (Slap, 1986). Most of the iron stores may be mobilized to meet growth needs (Pilch and Senti, 1984) and, in some cases, there may be no time for recovery of iron stores before menstruation begins.

Some contraceptive practices significantly affect menstrual iron losses. Intrauterine devices (IUDs) can double menstrual losses and result in lower serum ferritin and hemoglobin levels in users (Cole et al., 1971; Guillebaud et al., 1979; Kivijarvi et al., 1986). Alternatively, use of oral contraceptive agents can reduce menstrual losses substantially and permit greater iron stores (Cole et al., 1971; Frassinelli–Gunderson et al., 1985; Nilsson and Sölvell, 1967).
b. Gastrointestinal blood loss

Many lesions of the gastrointestinal tract may be responsible for blood loss. Hiatal hernia, esophageal varices, gastritis, duodenitis, peptic ulcer, cholelithiasis, intrahepatic bleeding, inflammatory bowel disease, diverticulosis, hemorrhoids, and gastrointestinal malignancies or adenomatous polyps are among the most common causes of gastrointestinal bleeding. Less common causes include vascular purpura with scurvy, aberrant pancreas, Meckel's diverticulum, hereditary hemorrhagic telangiectasia, other vascular ectasia of the bowel, and colonic polyposis (Brittenham, 1991).

Chronic use of aspirin also increases gastrointestinal blood loss. Mean blood loss was about 5 ml/day when four aspirin tablets (each equivalent to 300 mg acetylsalicylic acid) were taken (Pierson et al., 1961). This amount of blood loss is equivalent to 2 mg iron per day.

Other substances and medications whose chronic use frequently causes increased gastrointestinal blood loss include alcohol (Shaw and Lieber, 1988), some nonsteroidal anti-inflammatory agents in addition to aspirin (e.g., indomethacin, phenylbutazone, and naproxen) (Flower et al., 1985), and corticosteroids (Haynes and Murad, 1985).

c. Blood donation

Serum ferritin concentrations decrease following blood donation and decline progressively as frequency of donations increases (Finch et al., 1977; Simon et al., 1981). Data from these studies showed that about 8 percent of menstruating women who donated blood one time per year had depleted iron stores (serum ferritin <12 μg/L). The percentage increased with each additional donation, reaching a peak of 43 percent in menstruating women who donated blood five times per year (Skikne et al., 1984). Thus, the risk of anemia increases with more frequent blood donations.

Although some women are "superdonors" who, with or without iron supplementation, can donate blood frequently without becoming anemic (Monsen et al., 1983), iron lost through blood donation superimposed on basal and menstrual losses more often increases iron needs beyond the amount ordinarily supplied by diet. Iron supplementation of menstruating women who donated blood regularly has been shown to decrease the occurrence of depleted iron stores (Simon et al., 1981, 1984). Iron supplementation on the order of 15 to 30 mg/day should be recommended for all menstruating women who donate blood regularly.

2. Pregnancy

Because of the large amount of iron required to meet maternal and fetal needs during gestation, pregnant women are at risk of developing iron deficiency (Hallberg, 1988; Institute of Medicine, 1990). Slightly more than 1000 mg of iron is needed to meet the gestational iron needs for increased maternal red cell production and daily basal losses and for replacement of the permanent losses associated with pregnancy including loss to the fetus and placenta and blood loss at delivery (Hallberg, 1988). Women whose iron stores are minimal or absent at the beginning of pregnancy need to absorb almost 6 mg of iron each day during the second and third trimesters of pregnancy (Hallberg, 1988; Institute of Medicine, 1990). Maximal absorption of dietary iron by iron-depleted individuals has been shown to be about 25 percent (Monsen et al., 1983). Thus, absorption of 6 mg/day of iron would require that the diet contain at least 24 mg of iron, an amount that is not likely to be consumed, even with careful dietary selection.
Pregnancy during adolescence, particularly during early adolescence following reduction of iron stores by growth demands and onset of menstruation, further increases the risk for developing iron deficiency.

3. **Inadequate intake of bioavailable iron**

Because iron requirements are relatively high in relation to energy needs, some women may consume diets containing inadequate amounts of bioavailable iron. The amount of iron absorbed from the intestine is determined not only by the food iron content (amount and chemical form) but also by meal composition and the capacity of the gastrointestinal tract to absorb iron (Baynes and Bothwell, 1990). Complex interactions among these factors determine the adequacy of dietary iron intake (Monsen, 1988).

a. **Factors influencing absorption of iron**

Iron in food is present as heme and nonheme compounds in meats and as nonheme compounds in other foods. About half of the iron in meats (cellular animal products) is in the form of heme iron; the remainder is nonheme iron. Iron in plant foods and noncellular animal foods (e.g., eggs and dairy products) is in the form of nonheme iron compounds (Monsen, 1988).

Heme iron has high bioavailability; 15 to 35 percent is absorbed, the amount being inversely related to the iron stores of the individual (Monsen, 1988). Absorption of heme iron is enhanced by digestion products of dietary protein but is not affected by the inhibitors and enhancers that modify absorption of nonheme iron compounds (Layrisse and Martinez-Torres, 1972; Lynch et al., 1985).

In contrast to heme iron, only about 2 to 20 percent of nonheme iron is absorbed. However, because foods contain more nonheme iron, it usually contributes the greater proportion of total dietary iron. Its absorption is markedly affected by iron stores and by other compounds in foods consumed simultaneously with the iron-containing foods (Monsen, 1988).

Nonheme iron absorption is inhibited by polyphenols such as tannins in tea, coffee, and some sorghums; ethylenediaminetetraacetic acid (EDTA, a food additive used as a preservative and which chelates heavy metals); some calcium salts; phytates in cereals and legumes; and compounds in clay and earth which are consumed by some people (pica). Conversely, nonheme iron absorption is enhanced by consumption of ascorbic acid (or other organic acids such as citric and lactic acids) or meat, fish, or poultry in the same meal (Monsen, 1988). About 1 to 1.5 g meat is equivalent to 1 mg ascorbic acid for promotion of nonheme iron absorption (Hallberg and Rossander, 1984; Monsen et al., 1978). Investigations of Hallberg and Rossander (1984) indicate that dietary content of enhancers and inhibitors may produce as much as a tenfold variation in absorption of nonheme iron.

b. **Iron intakes of women of childbearing age**

Data from national surveys of food consumption suggest that intakes of dietary iron of women of childbearing age have averaged 10 to 11 mg/day, about 75 percent of which is nonheme iron (Life Sciences Research Office, 1989; Murphy and Calloway, 1986; Raper et al., 1984). Biochemical measurements of iron status in a nationally representative population (NHANES II, 1976–1980) indicated that about 10 to 14 percent of women 15 to 44 years of age had impaired iron status with or without anemia (Pilch and Senti, 1984). Taken together, these dietary and biochemical data
suggest that, on a population basis, mean consumption of about 10 mg iron/day is associated with adequate iron status in at least 86 percent of the women of childbearing age (National Research Council, 1989).

The mean iron requirement for women of childbearing age was recently calculated to be 11 mg/day, on the basis of total iron losses of 1.4 mg/day and 12.5 percent absorption of iron from a diet containing generous intakes of enhancing factors (protein and ascorbic acid) (Life Sciences Research Office, 1989). The recommended dietary allowance for iron (RDA) is 15 mg/day, assuming 10 to 15 percent absorption from diets typical for most industrialized countries. Consumption of 15 mg iron/day should result in absorption of 1.5 to 2.2 mg iron/day, amounts sufficient to replace the iron losses of most women (National Research Council, 1989).

Although the above information suggests that dietary iron consumption may be sufficient for most women of childbearing age, black women, those living below poverty, and those with less education tend to have somewhat lower mean iron intakes (Life Sciences Research Office, 1989). In all sociodemographic subgroups, women who have larger blood losses, those who usually consume low-calorie diets, and those who follow strict vegetarian diets (particularly those diets which are very restricted in enhancers of iron absorption such as ascorbic acid and meats) may have more difficulty consuming sufficient dietary iron to meet their needs. Dietary counseling about sources of iron, enhancing and inhibiting factors, and energy balance is recommended for these women.

B. SOCIODEMOGRAPHIC FACTORS

Population studies reviewed in Chapter III suggest that iron deficiency is more prevalent in certain sociodemographic subgroups. Univariate analyses of data from NHANES II and HHANES indicate that each of the following is a risk factor for iron deficiency in women 11 through 44 years of age:

- poverty;
- lower education level (less than a high school education);
- higher parity (three or more children); and,
- certain racial and ethnic backgrounds (black and Mexican American women) (Life Sciences Research Office, 1989; Pilch and Senti, 1984).

These risk factors are probably interrelated; however, specific relationships among them have not been determined.
V. DETECTION OF IRON DEFICIENCY ANEMIA IN HEALTHY NONPREGNANT WOMEN OF CHILD bearing AGE

A. RATIONALE FOR DETECTION OF IRON DEFICIENCY ANEMIA IN HEALTHY WOMEN

The most important priority in examining healthy nonpregnant women for iron deficiency is to detect iron deficiency anemia. Detection of this stage of iron deficiency was selected because, in the opinion of the Expert Panel, iron treatment of nonpregnant women should be used primarily to prevent the adverse physiological consequences associated with iron deficiency anemia.

Although mild iron deficiency without anemia can be detected by laboratory abnormalities in ferritin concentration, transferrin saturation, and erythrocyte protoporphyrin, this degree of iron depletion is less reliably diagnosed in individuals. The responses of laboratory abnormalities following treatment of mild iron deficiency with oral iron are variable and are not associated with measurable improvements in functional outcomes. Mild iron deficiency is often self-correcting (i.e., compensated by increased intestinal absorption of iron) and may not progress to anemia. The usefulness of detecting and treating mild iron deficiency without anemia has not been established.

Conversely, frank iron deficiency anemia is associated with adverse physiological consequences; specifically, exercise tolerance and work capacity are decreased in adults (Cook and Lynch, 1986; Dallman, 1982). The ready increase in hemoglobin concentration that occurs in response to iron treatment provides a means of evaluating the response and offers evidence that iron deficiency was the correct diagnosis (Fairbanks and Beutler, 1988).

B. RECOMMENDED APPROACH TO DETECT IRON DEFICIENCY ANEMIA IN WOMEN OF CHILD BEARING AGE

The Expert Panel recommended a two-step approach using measures associated with different aspects of iron deficiency (1) to screen for the presence of anemia and (2) to determine whether the anemia results from iron deficiency. Screening is used to sort out apparently well persons who probably have a disease from those who do not by means of a rapid and preferably inexpensive test. This step is intended to provide the presumptive identification of a disease rather than a diagnosis. A second test is required to make a positive diagnosis and assign probable cause in those persons who tested positive during screening (etiologic diagnosis) (Griner et al., 1981).

The approach recommended by the Expert Panel is outlined in Figure 2. Screening for anemia should be done for all apparently healthy women without clinical evidence of anemia at general health maintenance visits. Making an etiologic diagnosis in women who tested positive during screening applies only to healthy women. The approach recommended by the Panel applies only to the detection, treatment, and follow-up of anemia caused by uncomplicated iron deficiency in healthy women whose evaluation includes appropriate history and physical examination. These recommendations do not provide a scheme for the differential diagnosis or management of other causes of anemia.
GENERAL SCREENING

Hemoglobin Analysis\(^1\)
(All women of childbearing age
at general health maintenance visits)

\[ \begin{align*}
\text{Hemoglobin} &\geq 12 \text{ g/dL} \\
\text{No further testing} & \quad \text{for iron deficiency}
\end{align*} \]

\[ \begin{align*}
\text{Hemoglobin} &< 12 \text{ g/dL}\(^2\)
\end{align*} \]

ETIOLOGIC DIAGNOSIS

Serum Ferritin Analysis

\[ \begin{align*}
\text{Ferritin} &> 20 \text{ µg/L} \\
\text{Further evaluation} & \quad \text{Diagnosis of iron} \\
\text{for other causes of amenia} & \quad \text{deficiency anemia}
\end{align*} \]

\[ \begin{align*}
\text{Ferritin} &< 20 \text{ µg/L}
\end{align*} \]

\(^1\) Venipuncture sample preferred. If hemoglobin < 12 g/dL is obtained with a capillary sample, reevaluate with a venous blood sample.

\(^2\) Hemoglobin concentration < 10 g/dL is less likely to result from uncomplicated iron deficiency. In these cases, further investigation of etiology is indicated.

Figure 2. Schema for detection of iron deficiency anemia.
C. RECOMMENDED INDICATORS AND CRITERIA FOR INTERPRETATION OF TEST RESULTS

1. Screening for the presence of anemia

   a. Measurement of hemoglobin concentration

Measurement of hemoglobin concentration was recommended as the screening tool for iron deficiency anemia because it is the easiest of the essential iron proteins to measure and because of the likelihood that it reflects the production of other essential iron compounds (Dallman, 1986).

As shown by prevalence data from NHANES II (see Chapter III), about 10 percent of women of childbearing age in the general population have hemoglobin concentrations less than 12 g/dL (120 g/L). An analysis of the hemoglobin and iron biochemistry data from NHANES II using a more strict definition of iron deficiency (the MCV model) showed that routine hemoglobin screening was of greatest value when the prevalence of iron deficiency in a population was between 5 and 35 percent. According to this analysis, the sensitivity of hemoglobin concentration for detecting iron deficiency was 37 percent and its specificity was 93 percent (Binkin and Yip, 1990). Even though the sensitivity may seem poor, use of hemoglobin concentration to screen for anemia detects those women with more severe iron deficiency for whom treatment is more likely to be beneficial. Of the 50,000,000 women in the U.S. population between 20 and 44 years of age (Hollmann, 1990), about 5,000,000 would be expected to have hemoglobin concentrations less than 12 g/dL (120 g/L).

Hemoglobin concentration is also a good screening device for assessing general health status. Development of low hemoglobin concentration may occur before the appearance of other manifestations of serious illnesses including cancer and other chronic disorders such as liver disease, renal failure, and some endocrine disorders (Williams and Whelby, 1987). Thus, detection of low hemoglobin concentration in seemingly healthy women may provide an early indication of serious illness and indicates the need for further testing if iron deficiency is not confirmed as the cause of anemia.

   b. Criteria for interpretation of hemoglobin concentration

      i. Baseline criterion

Hemoglobin concentration below 12 g/dL (120 g/L) is the standard screening test to identify anemia in women (Bothwell et al., 1979). Similarly, the 5th percentile value for hemoglobin concentration from NHANES II for women between 20 and 44 years of age was about 12.0 g/dL (120 g/L). This value was considered the most appropriate cutoff to designate anemia in women of childbearing age by the Expert Panel.

The Expert Panel targeted women with hemoglobin concentrations between 10.0 and 12.0 g/dL (100 and 120 g/L) before adjustment for smoking and altitude (see below) as the group who would benefit from iron therapy. Hemoglobin concentration in this range is likely to be caused by uncomplicated iron deficiency. Hemoglobin concentration less than 10.0 g/dL (100 g/L) is more likely to have an additional cause such as chronic disease or blood loss and should always prompt a thorough investigation to determine the cause.

      ii. Adjustments for altitude and smoking

Analyses of NHANES II data indicated that persons living at higher altitudes have higher hemoglobin and hematocrit levels than those living at sea level (Centers for Disease Control, 1989).
Lower oxygen partial pressure at higher altitudes, reduction in oxygen saturation of blood, and a compensatory increase in erythrocyte production are factors contributing to a generalized upward shift of the hemoglobin and hematocrit distributions in these populations. Values for adjustment of hemoglobin and hematocrit for 1,000 foot increments in altitude have been derived from data collected by the CDC Pediatric Nutrition Surveillance System (PNSS) on children residing at various altitudes in the mountain states. Anemia will be underdiagnosed in individuals living at higher altitudes (e.g., Denver and Salt Lake City) unless there is an appropriate upward adjustment of the cutoff values by the amounts shown below.

<table>
<thead>
<tr>
<th>Altitude (feet)</th>
<th>Hemoglobin (g/dL)</th>
<th>Hematocrit (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3000–3999</td>
<td>+0.2</td>
<td>+0.5</td>
</tr>
<tr>
<td>4000–4999</td>
<td>+0.3</td>
<td>+1.0</td>
</tr>
<tr>
<td>5000–5999</td>
<td>+0.5</td>
<td>+1.5</td>
</tr>
<tr>
<td>6000–6999</td>
<td>+0.7</td>
<td>+2.0</td>
</tr>
</tbody>
</table>

Inhalation of carbon monoxide during smoking results in increased concentrations of carboxyhemoglobin which has no oxygen carrying capacity. Consequently, there is also a generalized upward shift of the hemoglobin and hematocrit distribution curves of smokers (Centers for Disease Control, 1989). Smoking-specific adjustments for hemoglobin and hematocrit derived from NHANES II data (Centers for Disease Control, 1989) are shown below.

<table>
<thead>
<tr>
<th>Cigarettes (number/day)</th>
<th>Hemoglobin (g/dL)</th>
<th>Hematocrit (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–20</td>
<td>+0.3</td>
<td>+1.0</td>
</tr>
<tr>
<td>21–40</td>
<td>+0.5</td>
<td>+1.5</td>
</tr>
</tbody>
</table>

The adjustments for altitude and smoking are additive for smokers living at high altitudes. For example, the hemoglobin cutoff value for a woman who lives in Denver (altitude of 5,280 ft.) and smokes 15 cigarettes per day would be adjusted upward by 0.8 g/dL or 2.5 percent hematocrit. If her hemoglobin were 12.5 g/dL, she would be anemic.

2. **Etiologic diagnosis of iron deficiency**

   a. **Measurement of serum ferritin concentration**

Although low hemoglobin concentration identifies women with anemia, it does not rule out causes other than iron deficiency such as thalassemias and some hemoglobinopathies as well as a variety of chronic illnesses (Fairbanks and Beutler, 1988). Serum ferritin concentration parallels total body iron stores (Addison et al., 1972) and its value as a measure of iron stores is widely acknowledged (Cook, 1982). For these reasons, measurement of serum ferritin concentration was viewed by the Expert Panel as the best overall single test for etiologic diagnosis of iron deficiency in a preselected population of anemic women.
Serum ferritin concentration is affected by the presence of infection and inflammation, cancer, and other chronic diseases but the effect of these conditions is to increase its concentration (Williams and Wheby, 1987). Anemia (low hemoglobin) in the presence of normal iron stores is an indication for further evaluation to identify other causes. A diagnosis of iron deficiency may be missed when one of these other conditions is also present.

The direct proportionality of serum ferritin concentration to total iron stores and its relative stability with repeated measurements in the same individual (Cook, 1982; Pilon et al., 1981) also make it a useful test to monitor iron repletion during treatment. Its measurement for diagnosis of iron deficiency provides baseline information for evaluating response to treatment.

An analysis of results of multiple measurements of iron status in a subset of female participants in NHANES II showed that about two-thirds of women with anemia (hemoglobin concentration <12 g/dL or 120 g/L) also had additional biochemical evidence of iron deficiency (Yip, 1990).

b. Criterion for interpretation of serum ferritin concentration

Serum ferritin concentrations less than 12 μg/L in adults are considered to represent total depletion of iron stores (Jacobs et al., 1972) and are unquestionably diagnostic of iron deficiency (Cook, 1982). For the purpose of confirming the presence of iron deficiency in women already identified as anemic by low hemoglobin concentrations, a cutoff of less than 20 μg/L was considered more appropriate than 12 μg/L for serum ferritin concentrations. Raising the cutoff value for serum ferritin increases the sensitivity (positive results in diseased persons) of the screening procedure at the expense of selectivity (negative results in healthy persons) (Griner et al., 1981). The prevalence of depleted iron stores will be increased in the preselected population receiving the ferritin test. Therefore, the predictive value of the serum ferritin is increased. Because serum ferritin concentrations are increased in the presence of infection and inflammation, use of 20 μg/L as the cutoff value also provides an allowance for elevation of low serum ferritin concentrations in cases where anemia and mild infection may both be present and helps to minimize false negative results.

D. ALTERNATIVE INDICATORS

1. Alternative for screening to detect anemia

If the measurement of hemoglobin concentration is not feasible, measurement of hematocrit (percent packed red cell volume) is an alternative screening tool for anemia. However, hematocrit determinations are subject to more sources of error than hemoglobin assays (Wheby, 1987). When hematocrits are used for screening, the cutoff value indicative of anemia in women is 36 percent, corresponding to a hemoglobin value of 12 g/dL. Hematocrit values less than 30 percent (10 g hemoglobin/dL) are less likely to result from uncomplicated iron deficiency and indicate a need for further evaluation. Additive adjustments to hematocrit for altitude and smoking were listed on p.16.

2. Alternatives for etiologic diagnosis: therapeutic trial or other laboratory tests

Alternatives to measurement of serum ferritin concentration are a therapeutic trial of oral iron or additional laboratory tests (transferrin saturation or erythrocyte protoporphyrin). The therapeutic trial consists of determining whether there is a rise in hemoglobin concentration after 6 weeks of administering a therapeutic dose of iron (120 mg/day). See pages 21–23 for details. There is a small prevalence of false positive results in the presence of concurrent inflammation which complicates the interpretation of a positive result in the erythrocyte protoporphyrin and transferrin saturation.
assays. In addition to iron deficiency, lead poisoning should be considered as a possibility when erythrocyte protoporphyrin is very elevated (>70 µg/dL RBC).

An alternative test for possible future use in the etiologic diagnosis of iron deficiency is the serum transferrin receptor assay. Levels of transferrin receptor in serum have been reported to provide a reliable index of iron deficiency anemia (Kohgo et al., 1986, 1987, 1988) and of early tissue iron deficiency (Skikne et al., 1990). Studies of sequential changes in circulating transferrin receptor during iron depletion indicated only small increases in receptor levels until storage iron was depleted; however, when serum ferritin concentrations reached subnormal levels, concentrations of serum transferrin receptor showed a much greater increase (Skikne et al., 1990). Because the serum transferrin receptor assay is influenced by changes in levels of functional iron compounds, it may provide a more sensitive means of detecting iron deficiency than currently available assays.

E. ADDITIONAL CONSIDERATIONS

1. Collection of blood samples

In clinical settings, hemoglobin concentrations are commonly measured on venous or capillary blood samples obtained by venipuncture or fingerstick, respectively. Hemoglobin measurements made on capillary samples have been reported to be more variable and significantly lower (Schifman et al., 1985), higher (Moe, 1970) or not significantly different (Lu et al., 1987) from those made on venous samples. Because of the many variables that affect sample collection, the Expert Panel recommended the use of venous blood samples for measuring hemoglobin concentration. A low hemoglobin value obtained on a capillary sample should be confirmed on a venous blood sample before a diagnosis of anemia is made.

2. Management of screening approach

The Expert Panel recognized that the performance of the hemoglobin and ferritin analyses may be managed in many ways. For example, the assays may be done at the same time or sequentially on a stored sample or on a sample obtained at a second visit. The preferred logistics will depend on the individual practice or clinic situation.

3. Cost-benefit considerations

The population of women 20 to 44 years of age in the United States numbers about 50,000,000 (Hollman, 1990). Thus, tests for the diagnosis of iron deficiency anemia in women of childbearing age represent a health care expenditure for a large number of persons.

Measurement of hemoglobin concentration is an integral part of any general health check and its use as a screening tool for anemia is not adding a costly test to detect a condition expected in only about 10 percent of women of childbearing age. Serum ferritin below 20 µg/L would be expected in about 30 to 35 percent of women between 20 and 44 years of age (Pilch and Senti, 1984). However, because low hemoglobin concentration is used to preselect the women who should have a ferritin test, only about 10 percent of women of childbearing age will receive a ferritin test.

The major documented benefit of treatment of iron deficiency anemia in adults is improved exercise tolerance and work capacity resulting from increased oxygen-carrying capacity (Viteri and Torun, 1974). Clinical and subjective impressions of an enhanced sense of well-being and increased vigor and appetite are often present after only a few days of treatment (Brittenham, 1991; Harris and Kellermeyer, 1970).
Higher hemoglobin concentrations in pregnant women are associated with improved exercise tolerance and better tolerance of blood loss at delivery (Hallberg, 1988). Possible beneficial effects on newborn infants include lower risk for low birth weight, prematurity, and perinatal mortality (Institute of Medicine, 1990).
VI. TREATMENT AND FOLLOW-UP OF UNCOMPPLICATED IRON DEFICIENCY ANEMIA IN NONPREGNANT WOMEN

A. OBJECTIVES OF TREATMENT

The objectives of treating women with iron deficiency anemia are twofold: (1) to reverse the anemia, as measured by the return of hemoglobin concentration to normal levels [>12 g/dL (120 g/L)] and (2) to build iron stores to protect against the recurrence of anemia. Because serum ferritin levels parallel total body iron stores (Cook and Skikne, 1982), replenishment of iron stores is evaluated best by measurement of the serum ferritin concentration.

B. RECOMMENDATIONS FOR TREATMENT AND FOLLOW-UP

The recommended strategy for reversing uncomplicated iron deficiency anemia is oral administration of a well-absorbed soluble ferrous iron compound with a defined follow-up schedule and dietary counseling. The schema for treatment and follow-up is illustrated in Figure 3.

1. Treatment

The Expert Panel recommended a two-part treatment strategy: (1) initiation of therapy with a relatively large dose of iron to reverse the anemia over a timespan of 6 weeks to 6 months, and (2) once the anemia is corrected, maintenance with a smaller quantity of iron to build stores and prevent recurrence of the anemia. The total timespan for therapy and follow-up should not exceed one year unless the ferritin concentration remains below 20 μg/L. The following specific recommendations were made.

- For therapy, the total daily dose should be 120 mg but can range from 60 to 180 mg. Iron should be taken in divided doses two or three times per day. Each dose should contain no more than 60 mg iron.

For maintenance, the total daily dose should be 30 mg but can range from 15 to 60 mg.

- Use of all oral iron preparations should be medically supervised.

- To maximize absorption, iron compounds should be taken alone, not as part of a multivitamin and mineral preparation or with other mineral supplements.

- To maximize absorption, iron should be taken with liquids such as water or fruit juice between meals or at bedtime. Beverages that inhibit absorption of supplemental iron (coffee, tea, or milk) should not be consumed at the time the iron is taken.

- Dietary counseling should provide patient education about forms, sources, and relative absorption of dietary iron. Effects of enhancers (ascorbic acid and meat, fish, and poultry) and inhibitors of nonheme iron absorption (e.g., coffee and tea and some calcium supplements) should be stressed.
Figure 3. Schema for treatment and follow-up of women with uncomplicated iron deficiency anemia.
2. Follow-up

Both the therapeutic and maintenance phases of oral iron treatment should be followed up and maintenance should not be extended indefinitely. Response to oral iron should be evaluated at 6 weeks and 6 months after initiation of therapy.

- After 6 weeks of oral iron therapy, the venous hemoglobin concentration should be measured in all patients.
  - If the hemoglobin concentration is >12 g/dL (120 g/L), reduction of oral iron to a maintenance dose (30 mg/day, range 15 to 60 mg) can be considered as early as 6 weeks. The continued presence of risk factors should be considered in deciding whether to extend the therapeutic dose for a longer time.
  - If the hemoglobin concentration has risen but has not yet reached 12 g/dL (120 g/L), the therapeutic dose should be continued.
  - If the hemoglobin concentration has not risen and patient compliance has been poor, a change in the iron compound or a lower therapeutic dose and additional counseling may be indicated. The hemoglobin concentration should be reevaluated at 12 weeks.
  - If the hemoglobin concentration has not risen and patient compliance has not been a problem, reevaluate the etiology for causes other than uncomplicated iron deficiency.

- After 6 months of oral iron treatment, the serum ferritin concentration should be measured.
  - If the serum ferritin concentration is >40 µg/L, oral iron treatment should be discontinued and the patient reevaluated at 1 year.
  - If the ferritin concentration is 20 to 40 µg/L, continued administration of maintenance levels of oral iron should be considered in terms of the continued presence of risk factors or underlying causes. For example, anemia resulting from heavy menstrual losses or regular blood donation is more likely to recur than anemia resulting from multiple pregnancies. Iron status should be evaluated again at 12 months.
  - If the ferritin concentration is <20 µg/L, the maintenance dosage of oral iron should be continued. Iron status should be evaluated again at 12 months.

Indications to discontinue oral iron treatment include the reversal of anemia if no critical risk factors are present, replenishment of iron stores, or the onset of menopause. After menopause, iron needs are decreased and pregnancy and menstruation no longer protect against manifestations of hereditary iron storage diseases.

C. EVIDENCE SUPPORTING TREATMENT AND FOLLOW-UP RECOMMENDATIONS

1. Use of oral iron preparations

A long history of use of soluble iron compounds administered orally has established the effectiveness of iron for reversal of iron deficiency anemia. Ferrous iron is more efficiently absorbed than ferric iron (Hallberg, 1970) and ferrous sulfate has been the iron preparation most often used for the treatment of anemia. Treatment is not limited to ferrous sulfate because ferrous fumarate and ferrous gluconate are also available (Drug Facts and Comparisons, 1987) and are absorbed about as
well as ferrous sulfate (Brise and Hallberg, 1962a). Total absorption of iron from any of these ferrous iron compounds at a specified dose is roughly proportional to its iron content (Brise and Hallberg, 1962a).

2. **Dose**
   
a. **Therapeutic dose**

The usual therapy for iron deficiency anemia is use of oral iron preparations at the level of 180 mg/day of iron, in divided doses. Clinical experience has demonstrated that this level of iron therapy produces an initial rapid increase in hemoglobin concentration followed by a slower correction of transferrin saturation and concentrations of erythrocyte protoporphyrin and serum ferritin (Brittenham, 1991; Wheby, 1980). While the Expert Panel recognized the efficacy of this level of iron therapy, they were also aware that a limited amount of clinical evidence indicating that lower doses ranging from 30 to 120 mg/day have been used effectively in reversing iron deficiency anemia (Chanarin and Rothman 1971; Brise and Hallberg, 1962a).

Although higher doses of iron result in a greater amount of iron being absorbed initially during oral iron treatment, the capacity of the intestinal mucosal cells to absorb iron diminishes quickly after oral iron treatment is begun. A slower hematologic response may occur with lower iron doses but a rapid response is not usually a critical aspect of treatment of iron deficiency anemia (Wheby, 1987). Lower doses are also less likely to produce gastrointestinal side effects (nausea, epigastric pain, constipation, and diarrhea) associated with use of oral iron treatment (Sölvell, 1970).

Doses of iron should be specified in terms of elemental iron rather than the particular iron compound. See Table 2 for examples of typical preparations containing iron alone in the United States and the amount of iron contained per dose.

**Table 2. Iron Content of Some Oral Iron Preparations.**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Elemental iron content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(weight percent)</td>
</tr>
<tr>
<td>Ferrous sulfate, anhydrous</td>
<td>30</td>
</tr>
<tr>
<td>Ferrous sulfate, hydrated</td>
<td>20</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>12</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>33</td>
</tr>
</tbody>
</table>

1 *Modified from Drug Facts and Comparisons, 1987.*
b. Maintenance dose

Indirect evidence for the adequacy of 30 mg/day of iron as a maintenance dose in nonpregnant women is provided by studies of Chanarin and Rothman (1971), Dawson and McGanity (1987), and Scott and Pritchard (1974). In these investigations, 30 mg/day of iron prevented anemia in pregnant women whose iron needs are higher than those of nonpregnant women.

3. Maximizing absorption of oral iron preparations

a. Interactions of supplemental iron and other nutrients

The efficacy of use of a soluble ferrous iron compound alone, (i.e., not as a part of a multinutrient supplement) is supported by studies of effects of other nutrients on iron absorption and studies of effects of supplemental iron on absorption of other essential minerals. Iron preparations containing additional nutrients may be more expensive and the additional ingredients may not improve or may even impede the correction of the iron deficiency.

The enhancing effect of ascorbic acid on absorption of dietary iron is well documented. However, absorption of supplemental iron is not similarly enhanced by addition of ascorbic acid, with the exception of a 200 mg dose of ascorbic acid which also produced epigastric pain (Brise and Hallberg, 1962b; Grebe et al., 1975).

Calcium and magnesium salts can significantly inhibit absorption of iron supplements. A recent study (Cook et al., 1991) showed that calcium carbonate at doses supplying 300 and 600 mg calcium did not inhibit the absorption of 37 and 18 mg supplemental ferrous sulfate when taken without food; however, both calcium citrate and calcium phosphate significantly reduced iron absorption from supplements when taken without food. All three calcium supplements significantly inhibited absorption of ferrous sulfate supplements when taken with food. Other studies of absorption of supplemental iron by pregnant women suggest that both calcium carbonate and magnesium oxide inhibit iron absorption (Babior et al., 1985; Seligman et al., 1983). Because of the inhibitory effect of some forms of calcium on iron absorption, women taking oral iron preparations and calcium supplements other than in the form of calcium carbonate should be cautioned against taking both supplements together.

High doses of iron have been shown to impair zinc absorption. Interference has been reported at doses greater than 25 mg iron (Solomons, 1988).

b. Administration of oral iron preparations

Oral iron preparations are better absorbed when taken between meals than when taken with meals (Ekenved et al., 1976; Hallberg et al., 1978; Layrisse et al., 1973). Side effects may be more likely when iron preparations are taken without food, although use of lower doses may lessen the problem since side effects are most likely with higher doses of iron (Hallberg et al., 1967; Sölvell, 1970).

Substances in foods that enhance or inhibit absorption of supplemental and food iron were discussed in Chapter IV. However, one point from that discussion should be emphasized here. Iron supplements should be taken with water or fruit juices. Beverages that inhibit iron absorption (coffee, tea, or milk) should not be consumed with oral iron preparations.
Because oral iron preparations should be taken without food, enhancing or inhibitory effects of particular substances in foods on absorption of supplemental iron are minimized. However, dietary counseling is recommended to educate patients about dietary practices contributing to better absorption of iron from foods which, in some cases, may decrease the need for continued use of supplemental iron.

4. **Expected time course of response to treatment**

A satisfactory rise in the hemoglobin level in response to iron administration provides strong evidence that iron deficiency was the cause of the anemia. If complicating factors do not slow the response to oral iron, hemoglobin concentration begins to increase after the first week and usually is normal in about 6 weeks. Replenishment of iron stores is a much slower process which does not begin until hemoglobin levels are normal (Wheby, 1980). Repletion of iron stores usually requires months of treatment because absorption of iron by the intestinal mucosa decreases as the anemia and iron deficiency are corrected (Wheby, 1987). Failure to obtain a complete response to oral iron treatment necessitates a further evaluation of the patient (Brittenham, 1991).

Iron deficiency anemia is likely to recur because the precipitating cause is often continuing, recurring, or simply not recognized. Thus, measurement of serum ferritin concentration after 6 months of oral iron is needed as an indicator of the extent to which iron stores have been built up. In combination with clinical judgment about the continued presence of risk factors, the serum ferritin response provides a means of evaluating the likelihood of recurrence of iron deficiency anemia and the necessity of extending oral iron treatment for a longer time. Follow-up at one year should be considered if risk factors cannot be alleviated.
VII. PROPHYLACTIC USE OF IRON SUPPLEMENTS AND DETECTION AND TREATMENT OF IRON DEFICIENCY ANEMIA IN PREGNANT WOMEN

Available information about prevalence of anemia in pregnant women in the United States and iron requirements during pregnancy was summarized in Chapters II and IV, respectively. The prevalence estimates for low-income high-risk pregnant women, though probably not representative of all pregnant women, are consistent with evidence that increased iron requirements during gestation are not readily supplied by diet alone.

The subject of iron nutrition during pregnancy was recently and comprehensively reviewed by the Subcommittee on Dietary Intake and Nutrient Supplements During Pregnancy (Institute of Medicine, 1990). That Subcommittee recommended the routine use of iron supplements for nonanemic women and the use of therapeutic doses of iron for iron deficiency anemia during pregnancy. Guidelines for use of oral iron supplements were also recently published by the International Nutritional Anemia Consultative Group (1989). The Expert Panel's recommendations regarding the prophylactic use of iron supplements and the detection and treatment of iron deficiency anemia during pregnancy are in agreement with those previous recommendations.

A. PROPHYLACTIC USE OF IRON SUPPLEMENTS

The results of several studies have shown that iron stores become depleted in women in western European countries during the second to third trimesters of pregnancy, even with use of iron supplements (Puolakkka et al., 1980; Svanberg et al., 1975a; Taylor et al., 1982) and it is reasonable to infer a similar situation for women in the United States (Institute of Medicine, 1990). Thus, low iron stores may be the physiologic norm for late pregnancy (Institute of Medicine, 1990).

Absorption of dietary nonheme iron increases as iron stores decrease during pregnancy (Svanberg et al., 1975b); however, even with enhanced absorption, the quantity of bioavailable iron in usual diets in the United States cannot provide sufficient iron to prevent anemia during pregnancy (see p. 10). Progression of depleted iron stores to mild or severe iron deficiency may be prevented by prophylactic use of iron supplements (Chanarin and Rothman, 1971; Dawson and McGanity, 1987; Puolakkka et al., 1980; Svanberg et al., 1975a; Taylor et al., 1982; Wallenberg and van Eijk, 1984).

Because of the increased likelihood of iron deficiency during pregnancy, the Expert Panel recommended daily use of oral iron supplements containing 30 mg of ferrous iron by all pregnant women during the second and third trimesters of pregnancy. Evidence supporting the prophylactic use of 30 mg iron during pregnancy comes from several therapeutic trials in which administration of 30 mg iron/day was as effective as higher iron doses for prevention of anemia in pregnant women (Chanarin and Rothman, 1971; Dawson and McGanity, 1987; Scott and Pritchard, 1974). Use of this relatively low dose of iron should result in fewer side effects during pregnancy since side effects are dose-related and have been described mainly with doses greater than 120 mg/day (Sövell, 1970). Iron should be taken with water or fruit juice and apart from meals to maximize absorption.

Guidance concerning the importance of dietary iron during pregnancy should be a part of prenatal care for all pregnant women. Beginning with the first prenatal visit, dietary guidance should emphasize the importance of consumption of iron-containing foods, the enhancing effects of meats, including fish and poultry and foods containing ascorbic acid and the inhibitory effects of coffee and tea on iron absorption when these foods and beverages are consumed at the same time as iron-containing foods. Consumption of nonfood items such as laundry starch or clay (pica) inhibits absorption of nonheme iron and this practice should be discouraged.
B. DETECTION AND TREATMENT OF IRON DEFICIENCY ANEMIA

Women with a greater likelihood of depleted iron stores prior to pregnancy (adolescents, regular blood donors, and women with large menstrual losses) are at higher risk for development of iron deficiency anemia during pregnancy. Likewise, women with sociodemographic risk factors (poverty, lower education level, higher parity, and black or Mexican American backgrounds) are likely to be at greater risk for development of anemia during pregnancy.

Because concentrations of hemoglobin and serum ferritin normally change over the course of pregnancy, different criteria are needed for the diagnosis of anemia in pregnant women. Normal hemoglobin values fall until about weeks 20 to 24 and then rise through the remainder of gestation. Anemia during pregnancy is defined as a hemoglobin concentration below the 5th percentile for healthy women of the same stage of pregnancy (Centers for Disease Control, 1989). Mean and 5th percentile values for hemoglobin concentrations at 4-week intervals throughout pregnancy are shown in Figure 4. These values are not adjusted for altitude and smoking. For clinical use, hemoglobin levels of 11.0, 10.5, and 11.0 g/dL (110, 105, and 110 g/L) should be regarded as the cutoff values for anemia in the first, second and third trimesters, respectively. Equivalent hematocrit cutoff values for hematocrit are 33.0, 32.0, and 33.0 percent, respectively (Centers for Disease Control, 1989). Adjustments for altitude and cigarette smoking should be made as described in Chapter V.

To detect extant anemia, hemoglobin concentration (or hematocrit) should be determined at the first prenatal visit. Based on the criteria specified in the paragraph above, a woman whose hemoglobin level is less than 11.0 g/dL (110 g/L) during the first or third trimesters and less than 10.5 g/dL (105 g/L) during the second trimester has anemia. If there is evidence of iron deficiency anemia at any time during pregnancy (low hemoglobin or hematocrit plus a serum ferritin concentration below 20 µg/L), a therapeutic dose of ferrous iron (60 to 120 mg iron/day with no more than 60 mg for any dose) should be given between meals or at bedtime to correct the anemia. This level of iron treatment should be continued until the hemoglobin concentration is within normal limits for the stage of pregnancy. At that time, the dose can be reduced to a maintenance level of 30 mg/day, again taken with water or fruit juice between meals or at bedtime.

![Figure 4. Hemoglobin values during pregnancy (Unpublished figure from R. Yip, Centers for Disease Control, 1989, with permission; Institute of Medicine, 1990, with permission).](image-url)
VIII. LITERATURE CITED


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