Iron depletion by whole-blood donation harms menstruating females:
The current whole-blood-collection paradigm needs to be changed

Bruce Newman

The collection of 450 or 500 mL of whole blood, plus an additional 30 to 50 mL for blood tests, results in 480 to 550 mL of blood loss per whole-blood donation. These losses lead to a 60- to 88-g loss of hemoglobin (Hb) per whole-blood donation in women, based on a Hb range of 12.5 to 16.0 g per dL, and 204 to 299 mg of iron loss, based on 3.4 mg of iron per gram of Hb. This iron loss is 9 to 13 percent of the total body iron in an average woman (2300 mg), and it is 66 to 97 percent of the total stored iron in an average menstruating woman (309 mg). Therefore, whole-blood donation is an iron depletion event that causes significant iron loss in women.

Menstruating women, even before blood donation, are at risk for iron depletion because of ongoing blood loss, recent pregnancies, and inadequate dietary iron. In Caucasian women, nonanemic iron deficiency is quantitatively defined as normal Hb concentration ($\geq 12$ g/dL), low ferritin ($\leq 12$ µg/L), and a second test that is consistent with iron deficiency. Iron-deficiency anemia is defined as the same, except the Hb concentration is less than 12 g per dL. A number of studies have been performed, mainly on adult women, to determine the effect of iron-deficiency anemia or nonanemic iron deficiency on one’s health. These studies have evaluated the effect of these two conditions on fatigue, physical endurance and work capacity, restless leg syndrome, adverse events related to pregnancy, and cognitive changes. Many of these studies have shown harm from iron-deficiency anemia and nonanemic iron deficiency.

The status of the current whole-blood-collection paradigm is to have a Hb cutoff that is slightly above the low end of normal in women and to not replace the iron that is lost during donation. This paradigm prevents severe anemia, but it does not prevent iron-deficiency anemia or nonanemic iron deficiency and their associated harms. A superior paradigm would be short-term iron replacement for menstruating women donors after successful whole-blood donation.

The present commentary will review the topic of iron deficiency in women, iron deficiency induced by whole-blood donation, and the harmful effects of the present collection paradigm (no iron replacement) on female donor health. It will then review early and recent studies on the use of oral iron supplements to replace iron after whole-blood donation, discuss an iron-rich diet versus short-term oral iron supplements, review issues related to iron supplementation, and review the potential of iron supplementation coupled with slightly lower Hb acceptance standards for women to increase the whole-blood supply.

IRON DEPLETION IN WOMEN

Fortification of food with iron has increased but has not prevented iron deficiency (or iron-deficiency anemia) in persons with a high need for iron such as infants, growing children, menstruating women, and pregnant women. The prevalence of iron deficiency in 20- to 49-year-old women before blood donation is 12 percent, based on 1999 to 2000 data from the National Health and Nutrition Examination Survey (NHANES 1999-2000), and it is as high as 22 percent in one ethnic group. The prevalence of iron deficiency decreases with the onset of menopause to 9 percent in 50- to 69-year-old women and to 6 percent in women older than 69 years. Approximately 4 percent of the 20- to 49-year-old women with iron deficiency also
have iron-deficiency anemia. In contrast, the prevalence of iron deficiency in 16- to 69-year-old men is 2 percent, and the prevalence of iron-deficiency anemia in men is less than 1 percent. Therefore, menstruating women have a much higher prevalence of iron deficiency than men. Correspondingly, ferritin concentration, which is a marker for iron storage, is also lower in 18- to 44-year-old women (309 mg) than in 18- to 64-year-old men (776 mg), which make women more susceptible to iron depletion from whole-blood donation.

A whole-blood phlebotomy removes Hb and Hb-bound iron. A greater relative proportion of Hb and Hb-bound iron is removed from women than from men because the whole-blood collection volume is fixed at approximately 525 mL, but women have smaller blood volumes than men because they weigh 35 to 40 lb less and have less muscle mass. Many women replace the iron lost over time through diet, but women with marginal or no iron stores and in negative iron balance do not replace the red blood cells (RBCs) lost and become anemic or iron-depleted.

**IRON DEPLETION FROM WHOLE-BLOOD DONATIONS**

Iron depletion induced by whole-blood donation has been evaluated in many studies. Repeat whole-blood donors have lower serum ferritin levels than first-time donors. In a composite of four studies, the mean serum ferritin level was 47 µg per L in repeat male donors versus 124 µg per L in first-time male donors, and the mean serum ferritin level was 25 µg per L in repeat female donors versus 46 µg per L in first-time female donors. Iron depletion is directly proportional to the frequency of whole-blood donation, but not to the number of whole-blood donations. In very frequent donors (six donations per year), ferritin levels decrease with the first four donations, irrespective of whether iron is supplemented, and then becomes stable. A composite of two studies, which evaluated iron depletion against the frequency of whole-blood donations per year, showed that iron depletion in menstruating women increased from 6 percent before donation to 19 percent after two donations and to 30 percent after four donations. Iron depletion in men increased from 0 percent before donation to 3 percent after two donations, to 8 percent after 4 donations, and to 19 percent after six donations per year. These data confirm that whole-blood donation increases the prevalence of iron depletion, that iron depletion is directly related to the frequency of whole-blood donations, and that the prevalence of iron depletion induced by whole-blood donation is higher in menstruating women than in men.

There is great variability in iron stores among individuals, but iron stores are stable within a single individual.

The initial ferritin level is predictive for iron depletion induced by whole-blood donation. Individuals with initial ferritins of greater than 10 mg per kg before whole-blood donation experience decreased ferritin levels with frequent blood donations but generally do not become anemic, whereas individuals with initial ferritins below 5 mg per kg often become anemic.

**Hb REGENERATION AFTER WHOLE-BLOOD DONATION**

Hb was restored at a mean of 7 weeks in 105 donors after a whole-blood donation of 555 mL. Seventy-four percent had regenerated their Hb to predonation levels by 8 weeks. The Hb regeneration time on subsequent donations was similar to that on the first donation. The Hb regeneration time was shortened to 5 weeks when oral iron was provided as a supplement, although the shortening of the regeneration appeared to decrease on the third and fourth donations. Ninety-three percent of the donors had regenerated their Hb to their predonation levels by 8 weeks when iron was ingested. The rate at which women regenerated their Hb, 0.040 g per dL per day, was less than for men, 0.049 g per dL per day. Other Hb regeneration studies support these findings.

**ADVERSE CLINICAL EFFECTS RELATED TO IRON DEPLETION INDUCED BY WHOLE-BLOOD DONATION**

The need for short-term iron replacement should be based on preventing harm to premenopausal women due to anemia or nonanemic iron deficiency induced by whole-blood donation.

**Relation of fatigue, decreased work productivity, and decreased physical endurance to iron depletion induced by whole-blood donation**

Studies show that iron-deficiency anemia is associated with fatigue, reduced maximal work capacity, increased work time per task, reduced endurance capacity, and decreased voluntary activity, and the incapacitation is in proportion to the degree of anemia. Nonanemic iron deficiency is associated with an increased prevalence of fatigue and decreased physical endurance, but the latter might only occur when iron depletion is at the tissue level. Individuals with tissue iron depletion become “anemic” relative to their own normal Hb concentration. For example, an individual with tissue iron depletion might have a Hb concentration of 12.7 g per dL but the individual’s normal Hb concentration is 14.5 g per dL. Tissue iron depletion is best measured with serum ferritin and the serum transferrin receptor (sTfR).
In 1000 whole-blood donors interviewed after whole-blood donation, the fatigue rate related to the blood donation was 7.8 percent, and it was 2.8 times higher in women (11.1%) than in men (4.0%; p < 0.001). The fatigue rate in women showed a trend (p = 0.065) toward being inversely related to female weight, but there was no association between fatigue and male weight. The higher fatigue rate in women might relate to greater iron deficiency, greater proportion of Hb removed, smaller female size, or a combination of these factors. Fatigue was associated with a 20 percent reduction in blood donor return rates at 1 year. Fatigue also impacts work productivity in workers, and affects childcare and leisure activities.

Three research groups in six studies showed that iron improved endurance in physically active women with nonanemic iron deficiency, but one research group found no change. Iron therapy shortened the time to complete a 15-km time trial, increased the total work rate, increased physical endurance, and decreased the percentage of maximal oxygen uptake. Studies by one research group found that iron increased Hb concentration and physical performance in subjects with nonanemic iron deficiency when the sTfR was high (≥8.0 mg/dL) but not in such subjects when the sTfR was low (3.5-7.9 mg/dL). In effect, high sTfRs differentiated between those who probably had anemia relative to their individual normal Hb concentrations and those who did not. Of the 41 physically active women with nonanemic iron deficiency, 14 or approximately one-third were found to have tissue iron deficiency (sTfR ≥8.0 mg/dL). Seven of these 14 women were given 16 mg of oral elemental iron per day for 6 weeks, and 7 were given a placebo. The 7 women prescribed iron improved their Hb level, physical endurance, and aerobic capacity, but the 7 women prescribed a placebo did not. Iron-depleted women with no tissue iron deficiency were also given the same regiment of oral iron supplementation and did not improve their Hb level, physical endurance, or aerobic capacity. These studies suggest that iron therapy is beneficial for women with nonanemic iron deficiency, when tissue iron deficiency (or "anemia") is present. The hypothesis is that iron is needed at the tissue level for the development of mitochondrial and myoglobin enzymes and that providing iron to persons with tissue iron depletion allows these enzymes to develop and leads to improvement in endurance and aerobic capacity. The study also suggests that previous studies of subjects with ferritin depletion and treated with iron were inadequate unless the study demonstrated that tissue iron depletion was present.

The restless leg syndrome and iron depletion induced by whole-blood donation

Iron-deficiency anemia and nonanemic iron deficiency have both been associated with the restless leg syndrome. The International Restless Legs Syndrome Study Group set four essential criteria for the diagnosis of restless leg syndrome in 1995, and the criteria were updated in 2003. These four criteria are: 1) urge to move the limbs associated with uncomfortable or unpleasant sensations in the legs; 2) motor restlessness worsens at rest; 3) urge to move is partially or totally relieved by activity; and 4) symptoms are worse in the evening or night or only occur in the evening or night. Restless leg syndrome is often associated with difficulty falling asleep and staying asleep; 80 percent of subjects with restless leg syndrome have periodic limb movements. The prevalence of restless leg syndrome is between 4 and 15 percent in Western populations, but it is much lower in Asian populations. Several but not all studies have reported a higher prevalence in women than men. Idiopathic and hereditary cases appear to be due to lack of dopamine, but iron depletion also causes restless leg syndrome. There may be a relationship between iron and dopamine because iron is a necessary cofactor for the production of dopamine, and abnormalities in transferrin activity have also been found. The prevalence of restless leg syndrome is higher in conditions associated with iron-deficiency anemia such as end-stage renal failure (20%-60%), pregnancy (20%-30%), and blood donation (14%-25%). Swedish studies found the prevalence of restless leg syndrome to be 6 percent in Swedish men and 11 percent in Swedish women, but a recent study in 946 consecutive repeat Swedish blood donors found the prevalence in 618 male donors and 328 female donors to be 15 and 25 percent, respectively. Swedish female donors, with iron deficiency determined indirectly through a high RBC distribution width (≥14.5), had a higher prevalence of restless leg syndrome of 37 percent. A limitation of the study was the comparison of the percentage of donors with restless leg syndrome to historical controls, as there was no control group. This is the only study of the frequency of restless leg syndrome in blood donors; no study has been performed in US blood donors.

Silber and Richardson also evaluated eight frequent whole-blood donors with restless leg syndrome and iron deficiency. Four had anemia and two had nonanemic iron deficiency. In six of eight donors, the donors’ symptomatology was related to starting whole-blood donations. Whole-blood donation either precipitated symptoms or enhanced them. Iron treatment resolved the symptomatology completely in three patients and decreased the symptomatology markedly in another two. All patients were advised to not donate blood to avoid further iron depletion.

Several studies have shown that the brain in restless leg syndrome patients often lacks iron, specifically in the substantia nigra and to a lesser degree in the putamen. There appears to be an inability in restless leg syndrome patients to bring ferritin from the blood into the brain.
brain. This finding has been established through imaging scans, which have shown lack of iron in the substantia nigra and putamen, through autopsy specimens that have shown lack of H-ferritin in the substantia nigra in comparison to controls, and through cerebrospinal fluid collections that have shown low ferritin in patients with restless leg syndrome. The severity of restless leg syndrome disease is inversely related to iron content in the substantia nigra. Oral iron has been an effective treatment, but iron injections are needed when patients have relatively high iron content (>40 µg/L ferritin) and fail to absorb much oral iron. Iron injections appear to be effective for approximately 6 months, but there is rapid excretion of iron or cellular overutilization because ferritin levels decline more rapidly than expected. Earley and colleagues were able to maintain restless leg syndrome patients after this decline with additional doses of intravenous iron gluconate.

Gastrointestinal blood loss workup and iron depletion induced by whole-blood donation

Low RBC volume in whole-blood units was observed several times per year in our blood center’s component laboratory when donor suitability was determined with an ear stick blood sample. Such observations became rare when our blood center switched from an ear stick to a finger stick blood sample. Finger stick blood samples provide a more accurate Hb concentration and are less variable than ear stick blood samples. Still, in a worst-case scenario, if a 110-lb, Caucasian iron-depleted woman with a Hb level of 12.5 g per dL, donates 525 mL of whole blood, the Hb concentration could decrease to 10.5 g per dL, which could lead to a physician visit for fatigue. The physician might evaluate the lower gastrointestinal tract by colonoscopy if the donor has no apparent external blood loss; if negative, an upper gastroendoscopy might be performed. The frequency of blood-loss evaluations and invasive procedures after whole-blood donations is unknown.

Adverse events in pregnancy and iron deficiency induced by whole-blood donation

Anemia (or iron-deficiency anemia) early in pregnancy causes an increase in preterm deliveries and lower-weight newborns. Scholl and associates found after controlling for confounders that women with iron-deficiency anemia have a twofold increase in preterm deliveries. Thus, women entering pregnancy with whole-blood donation–induced iron-deficiency anemia could have an increase in preterm deliveries and lower-weight newborns, and preterm infants are at risk for developmental delays.

Cognitive changes in adults and iron depletion induced by whole-blood donation

The relationship between iron-deficiency anemia, nonanemic iron deficiency, and cognitive changes in adults is unclear. In two recent abstracts, Murray-Kolb and coworkers and Beard and coworkers stated that both iron-deficiency anemia and nonanemic iron deficiency cause cognitive changes in adult women. One-hundred thirteen subjects who had iron-deficiency anemia or nonanemic iron deficiency were tested at baseline and after 16 weeks of oral iron supplementation. When women with the highest iron status were compared to women with the lowest iron status, women with high iron performed better on attention and memory tests. Women who improved their iron status over time also showed more improvement in attention, memory, and learning tasks in comparison to women who did not improve their iron status. The authors concluded that iron status is related to information processing in adult women.

Four others studies also reported positive findings, and four studies reported negative findings. Future cognitive studies of subjects with nonanemic iron deficiency should stratify by sTfR to determine whether tissue iron depletion is an important determinant for cognitive changes.

ORAL IRON: IRON-RICH DIET OR ORAL IRON SUPPLEMENTS?

Most blood centers encourage a high iron-rich diet for women who are rejected from whole-blood donation because of low Hb, and donors with hematocrit levels of 34 percent and below are often referred to their personal physicians for evaluation. Iron-rich diets, however, are relatively ineffective for iron replacement because 6 months or more are needed to increase ferritin levels by modest amounts, and such increases can only be accomplished with excellent dietary compliance. In contrast, oral iron supplementation is relatively quick and effective. In the first study to compare oral iron medication versus oral iron via diet, 44 iron-deficient women (ferritin level, <15 µg/L) were randomly assigned to receive either oral iron supplements (105 mg of elemental iron) or a high iron-rich diet for 12 weeks. They were compared with each other and against 22 iron-replete women (control group) at the end of 12 weeks and at 6 months. The mean serum ferritin in the women receiving oral iron supplements increased from 9.0 to 24.8 µg per L at 12 weeks and remained stable at 24.2 µg per L at 6 months. The women receiving an iron-rich diet and maximal encouragement to maximize compliance increased their ferritin levels marginally from 8.9 to 11.0 µg per L at 12 weeks and to 15.2 µg per L at 6 months. The iron-replete control group remained stable with ferritin levels of 49 to 51 µg per L at all time points. The study showed that oral iron supplements significantly increased ferritin levels within...
12 weeks, but an iron-rich diet had a minimal effect at 12 weeks and only a modest effect at 6 months, despite maximal encouragement. In another double-blinded study, 75 women with nonanemic iron deficiency were assigned to one of three groups for 16 weeks: 50 mg of elemental oral iron per day, placebo plus an intensive iron-rich diet, or placebo plus usual diet.  The oral iron supplementation group increased the mean serum ferritin levels from a baseline of 8.4 to 13.3 at 8 weeks and to 16.8 at 16 weeks. The high-oral-iron diet increased their mean serum ferritin level from a baseline of 10.3 to 11.7 at 8 weeks and to 14.0 at 16 weeks. The placebo group did not show a change in serum ferritin levels at either 8 or 16 weeks. Based on a multiple linear regression analysis, the oral iron supplement group increased their mean serum ferritin level by 59 percent, and the diet group increased their mean serum ferritin level by 26 percent at 16 weeks. The authors noted the difficulty of ensuring compliance with an iron-rich diet.  

These two studies show that oral iron supplementation is the method of choice and may be the only method that can increase ferritin levels in an iron-deficient population in a short time period. These data also suggest that current recommendations to increase dietary iron as a means of improving iron status may be ineffective.

**SHORT-TERM IRON REPLACEMENT WITH ORAL IRON: SUPPLEMENTATION AFTER WHOLE-BLOOD DONATION**

Short-term iron replacement refers to a period of oral iron supplementation after successful whole-blood donation to replace the iron lost. Many studies have evaluated the effect of oral iron supplementation on blood donors donating whole-blood and have found that oral iron supplements increase ferritin levels and Hb in iron-depleted populations such as menstruating women. 

Early studies evaluated the total iron dose necessary to replace iron after whole-blood donation and determined that the correct total dose was approximately 2000 mg of elemental iron delivered as a ferrous iron salt. In one recent study, 100 mg of elemental iron delivered in a ferrous iron salt over 20 days in regular blood donors produced rapid improvement in Hb in donors with iron-deficiency anemia, but there were no data on the frequency of side effects.  

Electrolyte doses of 39 or 40 mg per day as ferrous iron salts have been well tolerated, with minimal or no increase in side effects, and have been quite effective over an 8-week period. One-hundred milligrams of elemental iron delivered as carbonyl iron for 56 days was tolerated but still had a significantly higher percentage of gastrointestinal side effects in comparison to a placebo group. It is probable that the 5600-mg total dose could have been reduced significantly and still would have been effective. Other studies have reported a high percentage of gastrointestinal side effects with 180 mg of elemental iron per day via ferrous iron salt for 1 or 3 weeks and 1800 mg of elemental iron per day in a carbonyl form for 1 or 3 weeks. Simon and colleagues showed that there was no additional benefit by combining iron with vitamin C versus iron alone.

These results suggest that a 39 or 40 mg of iron sulfate dose (or equivalent carbonyl iron dose) for 8 weeks would be effective in the replacement of lost iron with minimal, if any, significant side effects. Carbonyl iron is safer than ferrous salt iron, but this additional safety may not be necessary due to unit-dose packaging (see below). Simon and colleagues also showed that iron supplementation (39 mg of elemental iron/day for 8 weeks) led to significant improvements in maintaining or increasing Hb and the ability to donate in comparison to control groups. They noted that women taking 39 mg of elemental iron for 8 weeks could increase their donation frequency and have donation frequencies that were equivalent to men.

A recent German study provided additional information on the effects of iron on women. Women were required to donate every 12 weeks over 6 months (three donations), and men were required to donate every 8 weeks over 6 months (four donations). The donors were stratified into treatment groups of no iron, 20 mg of iron per day, or 40 mg of iron per day, for 6 months. In 47 women donors not prescribed iron, ferritin levels decreased from 17.7 to 15.1 µg per L; the mean log of the sTfR factor/ferritin [log(TR/F)] increased from 1.39 to 1.55, which reflects increasing iron deficiency; and the iron deficiency rate (ferritin level, ≤12 µg/L) stayed constant at 49 percent after three donations. In 55 women donors prescribed 40 mg of iron per day, the mean ferritin level and log(TR/F) remained constant, but the percentage of women with iron depletion decreased from 55 to 34 percent after three donations. In 66 women donors prescribed 40 mg of iron per day, the mean ferritin level increased from 19 to 31 µg/L; the log(TR/F) decreased from 1.43 to 1.29; and the percentage of donors with iron depletion decreased from 39 to 14 percent, with almost all of the improvement (39% to 15%) after the first donation. The men were more stressed than the women because of a higher donation frequency, every 8 weeks versus every 12 weeks. When men were prescribed 40 mg of iron per day, they decreased their iron depletion rate from 26 to 13 percent after four donations, and most of the decrease in iron depletion occurred after the first donation (26% to 16%). The study showed that a 40 mg per day
iron dose not only replaces iron lost but also decreases the prevalence of iron deficiency within an 8-week period. Based on these studies, 40 mg of elemental iron per day for 8 weeks seems to be a reasonable starting point.

The studies just reviewed were performed in blood donors donating frequently or at the shortest allowed interval. Blood donation frequency is considerably less in a blood center. In a recent 1-year period (2004/2005) in the Detroit metropolitan area, 66 percent of the female donors donated one time per year, 22 percent donated twice per year, 8 percent donated three times per year, and 5 percent donated four or more times per year. A large blood center in Kansas city had similar results in 1982; 67 percent of the female donors donated one time per year, 22 percent donated twice per year, 8 percent donated three times per year, and 3 percent donated four or more times per year. Iron replacement should be more successful in regular female donors than in the described studies because of greater recovery time between blood donations.

**BENEFITS VERSUS RISKS OF IRON SUPPLEMENTATION**

The primary benefit of iron supplementation is elimination or amelioration of clinical conditions that relate to iron-deficiency anemia or nonanemic iron deficiency. These benefits include less fatigue, greater physical endurance, and more energy, which translates into more voluntary activity, increased child care, and greater work capacity. The prevalence of restless leg syndrome and its associated sleep disorders and discomfort would also decrease. Women donors would enter pregnancy with a lower frequency of anemia and would have a lower incidence of preterm deliveries and low-weight infants. Iron supplementation would also decrease the incidence of blood-loss workups and gastroendoscopies.

Risks related to iron therapy, however, were noted at a national workshop on maintaining iron balance in women blood donors in 2001. Some of these risks are no longer relevant, and the following discussion will address these issues.

**Masking of colon cancer**

Colon cancer should be considered when a patient presents with anemia. Long-term iron therapy for any reason could potentially mask a colon cancer, but short-term iron therapy to replace the quantity of iron removed would not because of its short-term nature and the limited amount of iron that is administered. Blood centers should promote short-term iron replacement therapy, not long-term iron therapy. The latter decision should be decided jointly by the donor and the donor's health care provider.

**Accidental poisoning of children**

Iron pills or capsules before 1997 were often issued in a pharmaceutical medicine container with a child-proof safety lock. There is potential for poisoning if a small child has access to the bottle and eats a large number of pills or capsules. Unit-dose packaging makes it more difficult to access pills, limits access to a large number of pills, and is designed to protect children under the age of 6. The US Food and Drug Administration required unit-dose packaging of iron supplements in 1997. Tennenbein analyzed the prevalence of iron ingestion and deaths in children under the age of 6 for 10 years before unit-dose packaging and for 5 years after unit-dose packaging. The data were based on the annual reports of the American Association of Poison Control Centers’ Toxic Exposure Surveillance System (TESS). Iron ingestion cases decreased by approximately one-third from 2.99 to 1.91 calls per 1000 calls to poison centers, and deaths decreased from 29 deaths in the preintervention period to 1 death in the postintervention period. The study suggests that children were still able to remove some iron tablets from their unit-dose packaging, but they were unable to remove a sufficient number to cause significant harm.

**Hemochromatosis**

Short-term iron therapy to replace the quantity of iron removed probably does not aggravate hemochromatosis because of its short-term nature and the limited amount of iron administered. Hemochromatosis, which was once thought to be a very common entity due to the high prevalence of homozygous HFE in Northern Europeans (1 in 200), is now thought to be rare. Recent studies have shown low penetrance for hemochromatosis in persons homozygous for the HFE gene, perhaps as low as 1 percent. In addition, HFE homozygous menstruating women have a lower risk for hemochromatosis than men or postmenopausal women because of ongoing menstrual blood loss. Therefore, hemochromatosis is rare in menstruating women, and short-term iron replacement probably does not increase the risk.
IRON DEPLETION BY WHOLE-BLOOD DONATION HARMs MENSTRUATING FEMALES

Gastrointestinal side effects
Iron therapy should be based on the donor’s desire to take iron supplements and should be individualized, if necessary. Approximately 25 percent of women in the United States already take some kind of iron supplement, but the dose might be low in some cases and not suitable for replacement of iron loss from a blood donation. Gastrointestinal side effects are related to iron dose and iron absorption characteristics. Symptoms can be minimized through the selection of an appropriate dose, by ingestion with 8 oz of water or juice, and through active management advice such as taking iron with food, if side effects become bothersome. As noted earlier, doses of up to 40 mg of elemental iron per day are well tolerated.

The interaction of iron with other drugs
Iron can interfere with the absorption of other drugs, and other drugs can interfere with the absorption of iron. The drug families with interactions relative to absorption include antacids, tetracyclines, fluorouracil aloneon, medications that affect gastric hydrochloric acid (e.g., cimetidine), ACE inhibitors, dimercaprol, etidronate, penicillamine, Aldomet, chloramphenicol, zinc supplements, and bile acid sequestrants. These drugs should be taken 2 hours before ferrous sulfate or 2 hours after ferrous sulfate; other iron compounds might have different time specifications. Iron may reduce the effectiveness of some medications such as levodopa and levothyroxine. Pharmacologic handbooks should be consulted for information on specific iron compounds.

The interaction of iron with foods
Ferrous sulfate is absorbed best when the stomach is empty. Gastric hydrochloric acid keeps the iron in the ferrous form, which is more soluble than the ferric form, and ferrous iron is absorbed better. Certain foods can interfere with nonheme iron absorption. They include green tea, coffee and tea, phytoestrogens (unleavened wheat products, wheat germ, nuts, oats, beans), whole wheat bran, eggs, soy protein, and calcium. Heme irons (found in meat), vitamin C, and vitamin A promote dietary iron absorption. Pharmacologic handbooks should be consulted for information on specific iron compounds.

The interaction of iron with other diseases
Iron can aggravate gastrointestinal tract ulcers, so iron may be contraindicated in donors with gastric or duodenal ulcers, inflammatory bowel disease, or other gastrointestinal conditions. Some precaution may also be necessary with alcoholic liver disease.

Atherosclerosis
The data on iron causing atherosclerosis are controversial. Nevertheless, short-term iron therapy to replace the quantity of iron removed should not affect atherosclerosis because of its short-term nature and the limited amount of iron administered.

Allergic reactions
Anaphylactic reaction after oral iron is very rare. Rarely, a donor could be allergic to sulfite or tartrazine, which are used in some iron preparations.

Cost-benefit ratio
Blood centers should supply an iron medication to donors. This provides control for the blood center and eliminates the need for the donor to visit a health care provider or to buy iron in a pharmacy. The increased convenience should lead to increased use. Improvements in whole-blood collections should far exceed a blood center’s cost relative to providing iron replacement therapy, but cost-benefit studies should be undertaken. In addition, all major metropolitan communities import blood during the year, and imports might not be available during parts of the summer or in early January. Additional units of blood provide an additional margin of safety.

THE BLOOD SUPPLY AND THE POTENTIAL EFFECTS OF SHORT-TERM ORAL IRON SUPPLEMENTATION COMBINED WITH ADJUSTMENTS OF Hb ACCEPTANCE LEVELS

Low Hb deferrals
Low Hb deferrals are responsible for approximately 40 to 75 percent of all blood donor deferrals, and 95 percent of the deferrals occur in women. Approximately two-thirds of low-Hb deferrals occur in women with Hb concentrations between 12.0 and 12.4 g per dL, which is the low end of normal for Caucasian females (12.0-16.0 g/dL) (see below). Iron supplementation could correct iron deficiency induced by whole-blood donation and normalize the donor’s Hb level within an 8-week period and without significant harm to those who are not iron-deficient. In the context of optimal Hb regeneration with iron, the Hb acceptance level could be safely lowered to 12.0 g per dL for Caucasian women, and consideration should be given to lowering the Hb concentration acceptance level to 11.3 g per dL in African American women. The term African American in this article refers to those individuals who regard themselves as being black African Americans. Numerous studies have shown that African Americans as a group have lower Hb concentrations than Caucasians (Figs. 1 and 2), and the general view is that these differences are mainly due to genetic differences between the two groups. Beutler and West in a very recent study evaluated 1491 African American and 31,005 Caucasian
subjects from an outpatient clinic. They evaluated hematologic data for the two populations and then in a stepwise fashion removed iron-deficient subjects, subjects with α-thalassemia, subjects with sickle-cell anemia, and subjects with high creatinine levels. By comparison of Hb differences at different points, one could surmise that 17 percent of the Hb difference between African Americans and Caucasians was due to greater iron deficiency in African Americans, but 83 percent of the Hb difference was genetic, with the bulk, 45 percent, being related to the high prevalence of α-thalassemia trait in African Americans. The study is the most definitive study to show that the differences in Hb between African Americans and Caucasians are mainly genetic. From a practical standpoint, the Hb acceptance standard needs to be lowered for African American women because the current Hb acceptance standard of 12.5 g per dL defers 38 to 43 percent of African American women, based on data from NHANES II (Table 1).

The goal for Hb deferrals should be to defer approximately 5 percent of women because of anemia related to menstrual blood loss, and 2.5 percent of the men because normal values include 95 percent of a group, with 2.5 percent on each end of the population distribution. Tables 1 and 2 show NHANES II data on Hb concentrations for Caucasians and African Americans between the ages of 18 and 44 years. The data are based on laboratory evaluation of 2582 Caucasian women, 385 African American women, 2397 Caucasian men, and 323 African American men. Table 1 shows that 16 percent of 18- to 44-year-old Caucasian women and 38 to 43 percent of 18- to 44-year-old African American women would be deferred based on a Hb acceptance standard of 12.5 g per dL. A decrease in the Hb acceptance standard from 12.5 to 12.0 g per dL for Caucasian women would decrease the deferral rate in Caucasian women by 55 to 58 percent and would increase the eligibility rate for Caucasian women by 9.0 percent. A decrease in the Hb acceptance standard from 12.5 to 11.5 g per dL for African American women would decrease the deferral rate in African American women by 63 to 75 percent and would increase the eligibility rate for African American women by 23.9 to 32.1 percent.

**TABLE 1. NHANES II data:** changes in deferral rates in menstruating women based on Hb acceptance cutoff levels

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<th>Hb concentration acceptance level (g/dL)</th>
<th>Age (Years)</th>
<th>Caucasian women ( % Deferrals)</th>
<th>African-American women ( % Deferrals)</th>
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<td>18-24</td>
<td>25-44</td>
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<td>Hb 12.5 g/dL</td>
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</tr>
<tr>
<td>Change in deferral rate (12.5 to 11.5 g/dL)</td>
<td></td>
<td></td>
<td>−62.6%</td>
</tr>
<tr>
<td>Change in eligibility rate (12.5 to 11.5 g/dL)</td>
<td></td>
<td></td>
<td>+23.9%</td>
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</table>
bility rate for African American women by 24 to 32 percent. The correct Hb acceptance standard in African American women, however, should be 11.3 g per dL (Table 1), and therefore eligibility rates would be even higher.

Table 2 shows inappropriately low donor deferral rates for low Hb in Caucasian men with a Hb acceptance level of 12.5 g per dL, but appropriate Hb deferral rates for African American men. Currently, anemic Caucasian men between Hb concentrations of 12.5 and 13.4 g per dL are being accepted for blood donation. The Hb acceptance standard for Caucasian men should be increased to 13.4 g per dL to prevent acceptance of anemic men. This step would increase the Caucasian male deferral rate by 2 to 3 percent (Table 2).

Beutler and Waalen recently determined the low end of normal for Hb concentrations in Caucasian and African American men and women from two large, recently gathered databases (NHANES III, 1988-1994; and Scripps-Kaiser database, 1998-2002). Iron-deficient donors were eliminated from the Scripps-Kaiser database based on laboratory tests. The authors concluded that the low end of normal for Caucasian women (age, 20-49 years) was 12.2 g per dL, and the low end of normal for African American women (age, 20-49 years) was 11.3 to 11.5 g per dL, based on a 5 percent lower end exclusion rate. They also concluded that the low end of normal for Caucasian men (age, 20-59 years) was 13.4 g per dL, and the low end of normal for African American men (age, 20-59 years) was 12.4 to 12.5 g per dL, based on a 2.5 percent lower end exclusion rate. These figures correlate well with the NHANES II database.

**Modification of Hb acceptance standards**

Hb acceptance standards for blood donors, with short-term oral iron supplementation in place, should be set at three different levels. The Hb acceptance standard should be 11.3 g per dL for African American women, 12.0 g per dL for Caucasian women and African American men, and 13.4 g per dL for Caucasian men. These standards are consistent with the low end of normal for these three groups. The proposed levels are slightly lower than the low end of normal for African American men, but using a 12.0 g/dL avoids having a fourth acceptance level for African American men. An alternative would be to have a fourth Hb acceptance level at 12.5 g/dL for African American men. As noted earlier, these acceptance standards will decrease donation eligibility in Caucasian men slightly (~2% to 3%), so that anemic Caucasian men will no longer be accepted, but will increase donation eligibility in Caucasian women (+9%), African American women (at least 24%-32%), and in African American men (+3%). It is probable that there is a large pool of women who want to donate blood but cannot overcome the current Hb acceptance standard of 12.5 g per dL, which acts as a barrier to them.

Two issues need to be considered when lowering Hb acceptance levels. First, lower Hb acceptance standards will result in lower Hb nadirs, which is particularly relevant for small women with low normal Hb concentrations. In the worse-case scenario, if a 50-kg woman, with a Hb concentration of 12.0 g per dL (Caucasian) or 11.3 g per dL (African American) donates 525 mL of blood, the Caucasian woman's Hb concentration would decrease (by 1.9 g per dL) to 10.1 g per dL, and the African American woman's Hb concentration would decrease (by 1.8 g/dL) to 9.5 g per dL. The Australians collected allogeneic blood for many years at a Hb acceptance standard of 11.5 g per dL, and did not recognize an increase in morbidity (A. Farrugia, written communication, December 2005). Autologous blood is also collected with a Hb acceptance standard of 11.0 g per dL. Therefore, slightly lower Hb acceptance standards for women appear to be safe. The second issue is the Hb dose obtained. The lower dose in some women would be countered by the slightly higher Hb dose obtained from Caucasian men (~13.4 g/dL). In addition, Hb dose is not standardized and current practice permits the highest dose obtained (500 mL, 18.0 g/dL) to be approximately 75 percent greater than the smallest dose obtained (450 mL, 12.5 g/dL).

Iron supplementation will permit a higher frequency of donation by women, and slightly lower Hb acceptance standards will permit greater female eligibility. Together, they have the potential to increase the RBC supply in the United States.

**CONCLUSIONS AND RECOMMENDATIONS**

Early researchers were aware of the decrease in ferritin after whole-blood donation and recommended iron ther-

<table>
<thead>
<tr>
<th>Hb concentration acceptance level (g/dL)</th>
<th>Caucasian men (% Deferrals)</th>
<th>African-American men (% Deferrals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb 12.5 g/dL</td>
<td>0.1%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Hb 13.5 g/dL</td>
<td>1.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Change in eligibility rate (12.5 to 13.5 g/dL)</td>
<td>-1.7%</td>
<td>+3.2%</td>
</tr>
<tr>
<td>Hb 12.0 g/dL</td>
<td></td>
<td>1.3%</td>
</tr>
<tr>
<td>Change in eligibility rate (12.5 to 12.0 g/dL)</td>
<td></td>
<td>+3.0%</td>
</tr>
</tbody>
</table>
A national workshop in 2001 considered iron for premenopausal women but did not recommend any broad actions relative to implementation of iron supplementation; rather, they recommended implementation of iron supplementation on a research or demonstration basis. The lack of broad action to implement iron supplementation widely was challenged in an editorial.

More information on donor harm relative to iron depletion and iron-deficiency anemia has become available since 2001. Harm relative to fatigue and decreased physical endurance has been better defined. Fatigue affects daily life and childcare, reduces work productivity, and decreases blood donor return rates by approximately 20 percent, and fatigue induced by whole-blood donation is more common in women than men. Whole-blood donation–induced anemia could also lead to presentation to a physician for fatigue, and the physician could elect to perform a blood loss evaluation, which could entail invasive gastroendoscopies. The restless leg syndrome is a newly identified risk for iron-depleted blood donors, and a recent Swedish study showed a much higher prevalence of restless leg syndrome in blood donors than in the general Swedish population. Restless leg syndrome is associated with discomfort and sleep disorders. Whole-blood donation–induced iron-deficiency anemia during early pregnancy is associated with a higher prevalence of preterm and low-weight infants, and the former is associated with an increased incidence of developmental delay. All of these described harms can occur on the first donation in an iron-depleted female. Therefore, these harms are best corrected with short-term iron therapy and not by reducing the frequency of whole-blood donation in women. Reducing the frequency of whole-blood donation might also have a negative impact on blood availability.

Short-term iron replacement is effective and safe therapy for blood donors who are iron-deficient and is not harmful to those who have adequate iron. Iron-deficient donors would increase their ferritin levels to above predonation values because of increased gastrointestinal iron absorption, which is an additional benefit. Many of the concerns relative to implementation of iron supplementation such as anemia masking, hemochromatosis, and poisoning of small children are no longer valid concerns, either because of the short-term nature of the iron therapy or because of advancements in technology (e.g., unit-dose packaging). Two-thousand milligrams of elemental iron (or slightly more) appears to be the correct total iron dose; 40 mg per day for 56 days provides 2240 mg and has been shown to be effective and well tolerated; it is a good starting point. Whether a better regimen exists will need to be determined. A fact sheet will need to be prepared to provide directions for oral iron use and to prevent iron interactions with certain drugs, diseases, and foods. Taking iron should be at the discretion of the donor, but iron should be recommended to all menstruating women to prevent harm.

Once short-term iron therapy is offered as an option to menstruating women, it would be reasonable to change the current Hb acceptance standard, as outlined above. Although Caucasian and African American women would be eligible to donate at slightly lower Hb concentrations, any risk would be more than counterbalanced by optimal Hb regeneration due to short-term iron therapy. In contrast, our present system does not provide iron and allows women to become iron depleted and in some cases to develop iron deficiency anemia. Just as important, a slightly higher Hb acceptance standard is indicated for Caucasian men because anemic men should not be accepted for whole-blood donation.

The Hb acceptance standard for women can be safely lowered with short-term iron therapy in place, and when it is, more Caucasian and African American women will be eligible to donate, and they will be able to donate more often because they will not be hindered by iron depletion. The potential increase in blood donations from inclusion of more women will far exceed the 2 to 3 percent loss from the elimination of anemic men. The net result will be an increase in the US blood supply capacity.

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