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Iron Replacement Therapy in the Routine Management of Blood Donors

Barbara J. Bryant[1,2], **Yu Ying Yau**[1], **Sarah M. Arceo**[1], **Jennifer Daniel-Johnson**[1], **Julie A. Hopkins**[1], and **Susan F. Leitman**[1]

[1]National Institutes of Health, Warren G. Magnuson Clinical Center, Department of Transfusion Medicine, 10 Center Drive, MSC-1184, Building 10, Room 1C711, Bethesda, MD 20892-1184

[2]University of Texas Medical Branch, Department of Pathology, Blood Bank Division, 301 University Boulevard, Galveston, Texas 77555-0717, Phone: 409-772-8284, Fax: 409-772-3193

Abstract

Background—Iron depletion/deficiency in blood donors frequently results in deferrals for low hemoglobin, yet blood centers remain reluctant to dispense iron replacement therapy to donors.

Study Design and Methods—During a 39-month period, 1236 blood donors deferred for hemoglobin <12.5 g/dL and 400 non-deferred control donors underwent health history screening and laboratory testing (CBC, iron studies). Iron depletion and deficiency were defined as ferritin of 9–19 mcg/L and <9 mcg/L in females and 18–29 mcg/L and <18 mcg/L in males. Deferred donors and iron-deficient control donors were given a 60-pack of ferrous sulfate 325 mg tablets, and instructed to take one tablet daily. Another 60-pack was dispensed at all subsequent visits.

Results—In the low hemoglobin group, 30% and 23% of females and 8% and 53% of males had iron depletion or deficiency, respectively, compared with 29% and 10% of females and 18% and 21% of males in the control group. Iron depleted/deficient donors taking iron showed normalization of iron-related laboratory parameters, even as they continued to donate. Compliance with oral iron was 68%. Adverse gastrointestinal effects occurred in 21% of donors. The study identified 13 donors with serious medical conditions, including eight with GI bleeding. No donors had malignancies or hemochromatosis.

Conclusion—Iron depletion or deficiency was found in 53% of female and 61% of male low hemoglobin donors, and in 39% of female and male control donors. Routine administration of iron replacement therapy is safe, effective, and prevents the development of iron depletion/deficiency in blood donors.

INTRODUCTION

Deferral of blood donors negatively impacts donor recruitment, donor retention and the ability to meet the growing demands on the blood supply. The most common cause of these deferrals is a screening hemoglobin value of less than 12.5 g/dL. Approximately 8–12% of donor visits result in a deferral for low hemoglobin each year.[1–3] Although the limited accuracy and reproducibility of current fingerstick hemoglobin screening methods contribute

Corresponding Author: Barbara J. Bryant, MD, bbryant@utmb.edu. Requests for Reprints: Barbara Bryant, corresponding author.

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to this process, a substantial number of these deferrals are a consequence of iron depletion in donors.

Short term studies conducted mainly in premenopausal female donors have demonstrated that oral iron supplements can prevent progressive decreases in hemoglobin and ferritin levels and reduce the incidence of deferrals for low hemoglobin levels during subsequent donation visits.[4–12] However, despite the favorable outcomes of these short term studies and the well-recognized and accepted fact that blood donations decrease body iron stores, blood centers are reluctant to dispense oral iron supplements to blood donors. Most blood center medical directors are unwilling to enter into a therapeutic relationship with donors due to insufficient time, limited medical screening and laboratory testing capabilities, lack of consistent follow-up, and an uncertain risk/benefit ratio.[13,14] Iron replacement therapy is therefore viewed as outside the role of the blood center.

The purpose of this study was to prospectively assess the incidence and operational impact of iron depletion/deficiency in blood donors and to evaluate the safety and efficacy of routine oral iron replacement therapy in donors 18 years of age and older.

MATERIALS AND METHODS

Donor Selection and Evaluation

The study was conducted as an Institutional Review Board-approved protocol at a single hospital-based donor center. Approximately 4500 unique donors make 12,000 visits per year at this facility, in order to donate 7000 whole blood (WB) units, 3500 plateletpheresis, and 1500 leukapheresis concentrates.

All donors deferred for a fingerstick hemoglobin value of less than 12.5 g/dL, but otherwise meeting AABB, FDA, and local blood center donor eligibility criteria, were approached to participate in the study. This constituted the “low hemoglobin group.” A concurrent group of “control donors” who were not deferred for a low fingerstick hemoglobin value were approached in order of presentation to the donor center during the first 12 months of the study, such that they comprised a 1:3 ratio with the low hemoglobin donors. Control donors were not matched for age, race, or gender. Exclusion criteria in both groups included age less than 18 years or a prior diagnosis of hemochromatosis. In addition, control donors were excluded if they were taking iron supplements.

All participants underwent health history screening and record review to determine blood donation frequency, history of low fingerstick hemoglobin values, current or past iron therapy, history of gastrointestinal or genitourinary blood loss, obstetric and gynecologic history, medications, diet, and personal or family history of anemia, clotting or bleeding disorders, hemochromatosis, hemoglobinopathy, or cancer.

Laboratory Testing

Capillary fingerstick hemoglobin values were obtained using a portable hemoglobin screening device (HemoCue Hb 201+, HemoCue, Cypress, CA). Samples for complete blood counts (CBC) were collected by venipuncture and analyzed by an automated hematology instrument (Cell-Dyn 4000, Abbott Laboratories, Abbott Park, IL). Serum iron determinations were performed on an automated chemistry analyzer (LX20, Beckman-Coulter, Inc., Brea, CA) as were ferritin and transferrin levels (Immulite 2500, Diagnostics Product Corporation, Los Angeles, CA). Transferrin saturation (%) was calculated as [Iron/Transferrin] × 71.2.

Oral Iron Replacement Therapy

Donors in the low hemoglobin group were given 60 tablets of ferrous sulfate 325 mg (65 mg of elemental iron) at the time of their deferral. Tablets were dispensed in child-resistant blister packs. Donors were instructed to take one tablet by mouth daily, 30 minutes before bedtime, with a half glass of water. Donors with a history of sensitivity to ferrous sulfate, or who developed intolerance to the tablets during the study, were given ferrous gluconate 325 mg tablets (38 mg of elemental iron). Subjects were instructed to notify a study physician promptly if adverse effects occurred.

Within 10 days of the initial visit, a study physician informed donors of their laboratory results and inquired about compliance with and tolerance to iron therapy. Control donors found to have iron deficiency (ferritin values below the reference range) were offered iron replacement tablets at the time they were notified of their laboratory results. Donors whose responses to health history screening questions and/or laboratory test results indicated a potentially serious health concern were referred to their primary care physician for follow-up.

Subsequent Donations by Study Donors

“Low hemoglobin” donors were deferred from subsequent WB donations for at least 60 days and apheresis donations for 30 days, following which they could be contacted by telerecruitment staff, whenever their names came up on routine telerecruitment lists. Subsequent donations were encouraged but not required. Interim medical history, assessment of oral iron compliance and tolerance, and laboratory evaluation were performed on all subsequent visits. Another 60-pack of iron tablets was dispensed at the time of each follow-up WB donation in order to offset the iron lost through donation. Since donation-related red cell losses were more modest in apheresis donors, iron replacement therapy was stopped when iron stores were replete, as reflected in a ferritin level exceeding 50 mcg/L in females and 100 mcg/L in males on two consecutive donation visits. Control donors were not given iron tablets at subsequent visits unless they had been found to be iron deficient on a previous donor visit.

Outcome Objectives

The primary outcome of the study was the safety of giving oral iron to male and female blood donors. The secondary outcome was efficacy, which was assessed as improvement in symptoms of iron depletion/deficiency, normalization of laboratory values, and decrease in the rate of deferral for low hemoglobin values. The incidence of symptomatic iron depletion/deficiency and the clinical response to oral iron will be described in a separate publication.

Statistical Analyses and Definitions

Iron deficiency was defined as a ferritin level below the institutional reference range of 9 mcg/L in females and 18 mcg/L in males; iron depletion was defined as a ferritin of 9 – 19 mcg/L in females and 18 – 29 mcg/L in males. We used two categories to describe low iron levels, in accord with prior studies of iron deficiency in donors. Levels below the reference range would be expected to cause iron-deficient erythropoiesis and symptomatic iron-deficiency anemia; this level was referred to as “iron-deficient.” Less extreme depletion of iron stores might be expected to cause milder symptoms and have lesser effect on erythropoiesis; this level was referred to as “iron depletion.”

Analyses were stratified by gender and donation type (WB versus apheresis) among the low hemoglobin and control groups. For some analyses, the low hemoglobin group was evaluated *in toto* since all subjects presenting with fingerstick hemoglobin values <12.5 g/dL were given iron replacement therapy. However, in order to demonstrate the safety of iron

replacement therapy in donors with low fingerstick hemoglobin values and ferritin values not indicative of iron depletion/deficiency, the low hemoglobin group was further stratified by initial ferritin levels. Group outcomes were compared using Student's t-test and proportions among groups compared using a Chi-square analysis for two by two contingency tables. When appropriate, paired t-tests were used, with statistical significance defined as $p<0.05$.

RESULTS

Donor Accrual and Donor Demographic Characteristics

During a 39-month period between 02/18/06 and 05/26/09, there were 40,422 visits to the blood center made by 7121 donors: 5651 WB and 1470 apheresis donors. Of these donors, 1236 deferred for low fingerstick hemoglobin values (1031 WB, 205 apheresis) and 400 control donors (366 WB, 34 apheresis) were enrolled. Enrolled donors represented greater than 90% of all donors deferred for low screening hemoglobin during the study period. The demographics of the 1636 protocol participants are shown in Table 1. Donors in the low hemoglobin group were significantly more likely than donors in the control group to be female (89 vs. 37%), African American (19 vs. 6%), and first time donors at the NIH (37 vs. 16%). Females in the low hemoglobin group were significantly younger than their counterparts in the control groups, whereas males were significantly older. Females in the low hemoglobin group were significantly less likely than control females to have made successful whole blood donations in the prior 12 months, due to the high proportion of first-time and previously-deferred females in the low hemoglobin group (1.3 ± 0.05 vs 1.8 ± 0.1 donations in the prior 12 months, respectively, $m \pm SE$, $p<0.001$). This was not true for males, wherein the number of donations in the prior 12 months did not differ among the low hemoglobin and control groups (3.2 ± 0.1 vs 2.9 ± 0.2 donations in the prior 12 months, respectively, $p=0.16$).

Laboratory Findings on Study Entry and Response to Iron Therapy

Initial fingerstick and venous hemoglobin values (mean ± SD) in the low hemoglobin group were significantly lower than those in the control group (fingerstick hemoglobin 11.8 ± 0.62 vs. 14.5 ± 1.20 g/dL, $p<0.0001$, and venous hemoglobin 12.3 ± 0.83 vs. 14.0 ± 1.05 g/dL, $p<0.0001$). Within the low hemoglobin group, initial fingerstick hemoglobin and ferritin values of females and males were similar (fingerstick hemoglobin 11.8 ± 0.62 vs. 11.9 ± 0.63 g/dL, and ferritin 29.3 ± 37.6 vs. 36.2 ± 47.4 mcg/L, respectively).

The prevalence of iron depletion and iron deficiency in the two donor cohorts at study enrollment is shown in Figure 1. Of the females in the low fingerstick hemoglobin group, 30% (318/1073) were iron depleted and 23% (244/1073) were iron deficient. These findings were even more striking in men in the low hemoglobin group, wherein 8% (13/163) were iron depleted and 53% (87/163) were iron deficient. A substantial fraction of control donors was also found to be iron depleted/deficient, with 29% (42/143) of females showing iron depletion and 10% (14/143) iron deficiency. Among male control donors, 18% (47/257) had iron depletion and 21% (54/257), iron deficiency. Overall, 54% of donors in the low hemoglobin group and 39% in the control group were iron depleted or deficient.

Association of fingerstick hemoglobin levels with iron status and with venous hemoglobin levels is detailed by gender in Tables 2 and 3. As expected, the incidence of iron deficiency increased with decreasing fingerstick hemoglobin levels with the exception of males in the 12.5–12.9 g/dL category, however, the number of subjects in this group was very small. Menopausal status did not significantly impact the iron status of female donors among the defined hemoglobin categories. Venous hemoglobin values, the gold standard of

hemoglobin determination, did not correlate tightly with fingerstick hemoglobin levels, which was especially evident at fingerstick hemoglobin levels just below 12.5 g/dL. More than 50% of women and 69% of men with fingerstick hemoglobin values in the 12.0–12.4 g/dL range had corresponding venous CBC hemoglobin levels greater than 12.5 g/dL, suggesting they should have met donor eligibility criteria. However, 46% of women and 56% of men in this group were found to be iron deficient or depleted.

Seventy-two percent of donors deferred for a low fingerstick hemoglobin and given oral iron replacement therapy returned for at least one subsequent visit. These donors showed steady and consistent improvement and normalization of iron-related laboratory parameters on subsequent donations, even as they continued to donate whole blood and apheresis components. Fingerstick hemoglobin, venous hemoglobin, mean corpuscular volume (MCV), red cell distribution width (RDW), serum ferritin, and transferrin saturation all normalized in this cohort (Figure 2). Donors in the control group who were given oral iron replacement for documented iron deficiency had a similar response (Figure 3B–D). However, ferritin levels in the control donors not on iron therapy steadily declined with each additional blood donation, despite relative preservation of fingerstick and venous hemoglobin values (Figure 3A).

In the apheresis group, 7 of 218 apheresis donors given oral iron reached a protocol-specified treatment endpoint of ferritin greater than 50 mcg/L in females or greater than 100 mcg/L in males. Iron was discontinued in these donors.

Safety of Oral Iron Replacement Therapy

Oral iron supplements were given to 574 donors (46% of the low fingerstick hemoglobin group) who were subsequently found to have ferritin levels that were not indicative of iron depletion/deficiency. Fifty-four percent (310 of 574) of these donors had venous CBC hemoglobins greater than 12.5 g/dL, suggesting that an inaccurate fingerstick value accounted for a large proportion of these findings. Iron supplementation in this group of 574 iron-replete donors was associated with a sustained increase in fingerstick hemoglobin of approximately 1g/dL on subsequent visits (Figure 4A). Serial laboratory monitoring as the donors continued to take oral iron and donate whole blood demonstrated stable ferritin levels that fluctuated around the initial value, but did not show an upward trend (Figure 4B). Continued iron replacement therapy did not result in iron overload in any donor. A small group of 29 female donors continued to show fingerstick and venous CBC hemoglobins that were less than 12.5 g/dL despite oral iron ingestion. Hemoglobins in this group were all within the reference range for our laboratory (11.1 – 15.0 g/dL), and appeared to be due to a physiological hemoglobin set-point on the low end of the normal range. No donors were found to have ferritin and transferrin saturation levels suggestive of hereditary hemochromatosis.

Careful health history screening and attention to laboratory results during the course of the study led to the diagnosis of several serious medical conditions in participating donors. Eight donors were referred to their personal physicians after occult gastrointestinal bleeding was suspected based on information elicited during the health history screen (seven cases) or the donor experienced a sudden and unexplained drop in hemoglobin (1 case). Five donors were diagnosed with gastritis and three donors were found to have lower gastrointestinal bleeding of nonmalignant etiology. Two donors were diagnosed with vitamin B12 deficiency after successful iron replacement therapy revealed elevated MCV levels (greater than 103 fL) and prompted laboratory orders for vitamin B12 and folate levels. One case of hyperthyroidism with thyrotoxicosis was diagnosed by the study physician after an elevated ferritin level led to additional donor questioning and testing. An incidental diagnosis of essential thrombocythemia was made in a donor with a platelet count of 1400×10^9/L, and

early stage myelodysplastic syndrome was diagnosed in a regular blood donor with decreasing hemoglobin levels. Other medical conditions diagnosed by health history screening and/or laboratory testing included uncontrolled diabetes mellitus (5 cases; 2 previously undiagnosed), hematuria of unknown cause (1 case), substance abuse (1 case), anemia due to profuse epistaxis requiring surgical intervention (1 case), Raynaud's syndrome (1 case), and hemoglobinopathies (numerous). Severe iron deficiency anemia was diagnosed in 2 donors who had undergone gastric bypass surgery greater than 5 years ago and in 1 donor with complete gastrectomy for gastric ulcers 40 years earlier. In all of these cases, donor evaluation by blood center staff prompted rather than masked a diagnosis. During the period of the study, no donors were found to have occult colorectal malignancies.

Compliance with Therapy and Adverse Effects of Oral Iron

Compliance with oral iron replacement therapy was defined as the percentage of the 60 tablets of iron taken before the next donation visit or the percentage of daily iron tablet ingestion for apheresis donation intervals less than 60 days. Compliance with iron therapy was 68% (range 0–100%) during the 39-month study. Oral iron tablets were given to 1362 donors (1200 low hemoglobin group and 162 control group) meeting study criteria. Upon study entry, 80% (1084/1362) of these donors received ferrous sulfate. The remaining 20% of donors (278/1362) reported prior intolerance to ferrous sulfate and were given ferrous gluconate at entry into the study. Of the donors receiving ferrous sulfate, subsequent intolerance that was bothersome enough to require a switch to ferrous gluconate developed in 21% (231/1084) of subjects. Overall, only 5% of donors (68/1362; 44/1084 initially given ferrous sulfate and 24/278 or 9% of those initially given ferrous gluconate) were intolerant to both ferrous sulfate and ferrous gluconate and discontinued the study's iron replacement therapy. The degree of intolerance was graded as severe in 30% of the events reported (74/279 and 47/127 in the ferrous sulfate and ferrous gluconate groups, respectively) and was predominantly gastrointestinal in nature (96% of all events), with constipation being the single most common complaint (Table 4). Of the donors reporting adverse effects to iron replacement therapy, 17% (47/278) and 47% (59/127) of the donors taking ferrous sulfate and ferrous gluconate, respectively, felt their symptoms were mild enough to continue the iron replacement therapy as prescribed.

In the low hemoglobin group, 36 donors (36/1236, 3%) declined to take the iron tablets provided by the study. This was attributed primarily to personal preference in selection of iron tablets (desire to purchase their own tablets similar to those used in the study), need for Kosher or strict vegetarian iron formulations, or refusal to take iron tablets once enrolled (accounting for some of the subjects reporting 0% compliance with therapy).

Long Term Donor Center Operational Effects of Routine Iron Replacement

During the study period, the average interval between donor visits in the low hemoglobin group was 92 days for females and 76 days for males. In the control group, the interval was 94 days for females and 81 days for males. Overall in the study, the interval between donor visits was 87 days; 92 and 79 days for females and males, respectively.

During the study period, the average productive (non-deferred) donor visits per donor per year was 1.3 for our entire whole blood donor population (1.1 and 1.6 for females and males, respectively) versus 1.9 for those enrolled in the study (1.5 and 2.8 for females and males, respectively). However, the percent of all visits that resulted in a deferral for low fingerstick hemoglobin was slightly though not significantly higher in the study population than in the entire donor population. Donors participating in the oral iron replacement protocol did not achieve a decrease in their low-hemoglobin deferral rate, but they returned to the blood center more frequently to attempt donation, which resulted in a 46% increase in

productive visits per donor per year compared to the general donor population. Thus donors in the “low hemoglobin group” who received oral iron replacement donated more units of whole blood per year than the general population of whole blood donors in our center.

DISCUSSION

Iron depletion in first-time and repeat blood donors is a challenge in transfusion medicine. With each whole blood donation, men lose 242 ± 17 mg and women lose 217 ± 11 mg of iron.[14] Given that normal iron stores in men and women are 1000 mg and 350 mg, respectively, iron balance can be difficult to maintain in a donor population. Inadequate dietary iron intake often fails to reestablish iron balance in blood donors. This was apparent in the control population of this study, in which a steady drop in serum ferritin level was seen with each additional whole blood donation, and did not stop until oral iron therapy was introduced. Hemoglobin determinations on fingerstick capillary samples are not robust indicators of the status of body iron stores, both because of the imprecision of the technique and because changes in hemoglobin are a late manifestation of iron deficiency. Our study reflected these problems: 54% of donors deferred for a fingerstick hemoglobin below 12.5 g/dL were iron deficient or depleted, however, 39% of donors “passing” the fingerstick hemoglobin screen were also iron depleted/deficient. Although our study was not designed to assess the appropriateness of current hemoglobin eligibility thresholds in U.S. blood donors, it was notable that 62% of male donors with a screening hemoglobin of less than 13.0 g/dL were iron depleted or deficient.

Data from the REDS-II Donor Iron Status Evaluation (RISE) study support our findings and confirm the high prevalence of iron deficiency in frequent blood donors. This 2-year NHLBI-sponsored study, conducted at six blood centers in the United States, evaluated the iron status of 2425 male and female blood donors. Ferritin levels of less than 12 mcg/L were used to define absent iron stores and log serum transferrin receptor (sTfR)/ferritin of 2.07 or greater was used as a marker of iron-deficient erythropoiesis. The RISE study found 15% and 42% of blood donors had absent iron stores and iron-deficient erythropoiesis, respectively. In men donating WB (or equivalent double red cell donations) three or more times and women donating two or more times in the prior year, 49% of men and 66% of women were iron deficient.[15,16] Iron deficiency is a common finding in blood donors.

Our data, as well as the RISE findings, provide a strong rationale for establishing policies whereby all blood donors, regardless of fingerstick hemoglobin value, are counseled and given a replacement pack of oral iron tablets. If they “pass” hemoglobin screening and donate blood, the iron “replaces” what they have just lost. If they do not “pass” screening, the iron is likely to replace what they lack. Administration of one tablet of 38 to 65 mg of elemental iron daily, in the form of ferrous gluconate or sulfate, was well tolerated in our study, with only 5% of subjects intolerant to both formulations. Since tolerance of ferrous gluconate was better than ferrous sulfate (9% vs 21% intolerance to initial treatment, respectively), blood centers may prefer to use the gluconate preparation in order to maximize compliance. The child-proof blister packs in which all iron supplements are currently packaged considerably lessen the concern for inadvertent overdose in young children.[17,18] Absorption of 5–10% of the ingested dose per day for 60 days supplies the amount of elemental iron lost in a single unit of blood.[19] The success of this replacement schedule was reflected in a marked and consistent rise in ferritin levels and normalization of accompanying markers of iron depletion and deficiency in the donors in this study.

One repeatedly cited risk of iron replacement in blood donors is the possibility of masking an underlying malignancy.[13,14] The incidence of colorectal cancer in adults is 1 in 2,000 for all ages, sexes, and races, and rises to 1 in 250 in males over age 70.[20] This rate might be

even higher in subjects presenting with iron deficiency anemia. No cases of gastrointestinal cancer were discovered during the course of this study. Our donor evaluation process easily allowed us to identify subjects requiring referral to personal physicians for more comprehensive work-up. Rather than posing a risk of harm to the donor, it is more likely that early attention to iron depletion/deficiency would lead to earlier detection of occult malignancy and a higher chance of cure.

Several donors with serious medical conditions were identified in this study and referred to their personal physicians for evaluation. Close supervision of iron-deficient donors, accomplished as described in the protocol by both blood center medical staff and by referral to personal physicians, revealed that blood losses due to prior blood donation, genitourinary losses related to menstruation and pregnancy, gastrointestinal losses due to nonmalignant lesions, epistaxis, and dietary deficiency of iron due to poor diet or vegetarian lifestyle accounted for 100% of the cases of iron-deficiency or depletion in blood donors.

The most common cause of a fingerstick hemoglobin less than 12.5 g/dL, confirmed by venous CBC hemoglobin, in donors found not to have iron depletion/deficiency and not responsive to iron therapy was a low set-point, a physiologically normal hemoglobin that was less than 12.5 g/dL. Donors in this category were universally female and had hemoglobin levels within the reference range, but on the border of donor acceptability (12.0 ± 0.5 g/dL). If allowed to continue to try to donate, such donors demonstrated a deferral rate of greater than 50%. Donors with greater than 80% deferral rates for low hemoglobin values due to a physiologically low hemoglobin were advised to discontinue blood donation. Donor frustration over continued non-successful donor visits was avoided in this manner, and female donors with lower normal hemoglobin levels were reassured that, although they did not meet criteria for blood donation, their hemoglobin was still within the normal range for females.

A frequently cited concern related to iron replacement in donors is that a person with hemochromatosis might be given iron tablets.[13,14] Published data show that it is extremely unlikely for healthy, undiagnosed hemochromatosis subjects to present with low hemoglobin values.[21] The population frequency of genetic hemochromatosis, 1 in 200 Caucasians of northern European descent, suggests that we should have seen 3 to 4 subjects with hemochromatosis among the 832 Caucasians in our “low hemoglobin” group. The fact that none were detected despite careful screening with ferritin and transferrin saturation levels supports the improbability of having an untreated hemochromatosis subject present to a blood center with a hemoglobin less than 12.5 g/dL.

The role of iron in the development of cardiovascular diseases has been widely debated since Sullivan first proposed the “iron hypothesis” in 1981, which theorized that iron depletion may provide protection against cardiovascular events.[22] Several studies have demonstrated a positive association between increased body iron stores and the risk of developing coronary heart disease, carotid atherosclerosis, and peripheral artery disease .[23–28] However, many epidemiological studies do not support this association.[29–35] In our study, the iron given to donors was only enough to replace the iron lost from blood donation, thus returning the donor to their pre-donation iron status. In addition, most donors receiving oral iron supplementation maintained ferritin levels in the lower quartile of the reference range.

One of the goals of the study was to demonstrate the effect of oral iron replacement on subsequent deferrals for low hemoglobin in the donor population as a whole. We found that iron replacement therapy was not associated with a decrease in overall donor deferral rates. This observation is confounded by several variables. In some donors, more than 60 days of

iron therapy was needed to restore hemoglobin levels to ≥ 12.5 g/dL. Nearly 40% of female donors returning 60 days after their initial deferral had incomplete repletion of iron stores. In addition, donors with iron depletion or deficiency who were given oral iron replacement tended to return more frequently than they had prior to study enrollment. This observation confirms the findings of Gillon and colleagues who reported that willingness to participate in an iron replacement protocol was an independent predictor of return visits to the blood center and thus resulted in overall higher deferral rates since more deferred donors were returning in an effort to donate.[36] The deferral rate in their iron replacement group was nearly double that of the overall study population, however, the number of donations/donor/year was not significantly different, reflecting their higher rate of donation attempts. Similarly, we found that overall deferral rates did not decrease in donors participating in our study; however, the number of productive visits per donor per year increased 46% above the general donor population. Overall, the iron replacement protocol had a measurable positive operational effect for the blood center.

The advantages to the donor center of establishing iron replacement programs to correct and maintain acceptable hemoglobin and ferritin levels in first-time and repeat donors are evident. Advantages include improved donor retention, prevention of symptomatic iron depletion/deficiency in repeat donors, and recognition by the community of the public service being provided. Cost of a program such as the one described in this study consists primarily of personnel expenses. Physician oversight is required to order and interpret laboratory tests and to prescribe iron. Health professionals are needed to facilitate medical history screening, promote compliance, assess intolerance to therapy, order and collect laboratory samples, and maintain databases. The tangible cost per donor enrolled in the study was less than $12 per visit, including laboratory testing ($10) and 60 tablets of iron ($1.40). These costs could easily be offset by the benefits of a successful program. The cost of recruiting a new blood donor is estimated to be $50-$400 (Department of Transfusion Medicine, NIH data), thus donor retention is less costly than donor recruitment. If a donor center does not have the financial/personnel resources to institute an iron replacement plan such as the one described in this study, our data support the following approach to iron management in the donor center. Oral iron replacement with a formulation that contains at least 38 mg of elemental iron, taken once daily for 60 days, may be offered to all donors, male and female, with screening hemoglobin levels <12.5 g/dL and a history of prior blood donation, and to all premenopausal females with hemoglobin <12.5 g/dL.

Blood Centers are confronted with the challenges of both pre-existing iron deficiency/depletion in blood donors and iron depletion/deficiency caused by blood donations. Iron replacement programs are a win-win proposition for both donors and donor centers. The data from this study support the safety and efficacy of iron replacement as a routine practice in all blood donors, including those who donate and those who are deferred. In the not too distant future, donors may find that “donor iron” is as helpful and desirable as “donor cookies” in maintaining well-being following blood donation.

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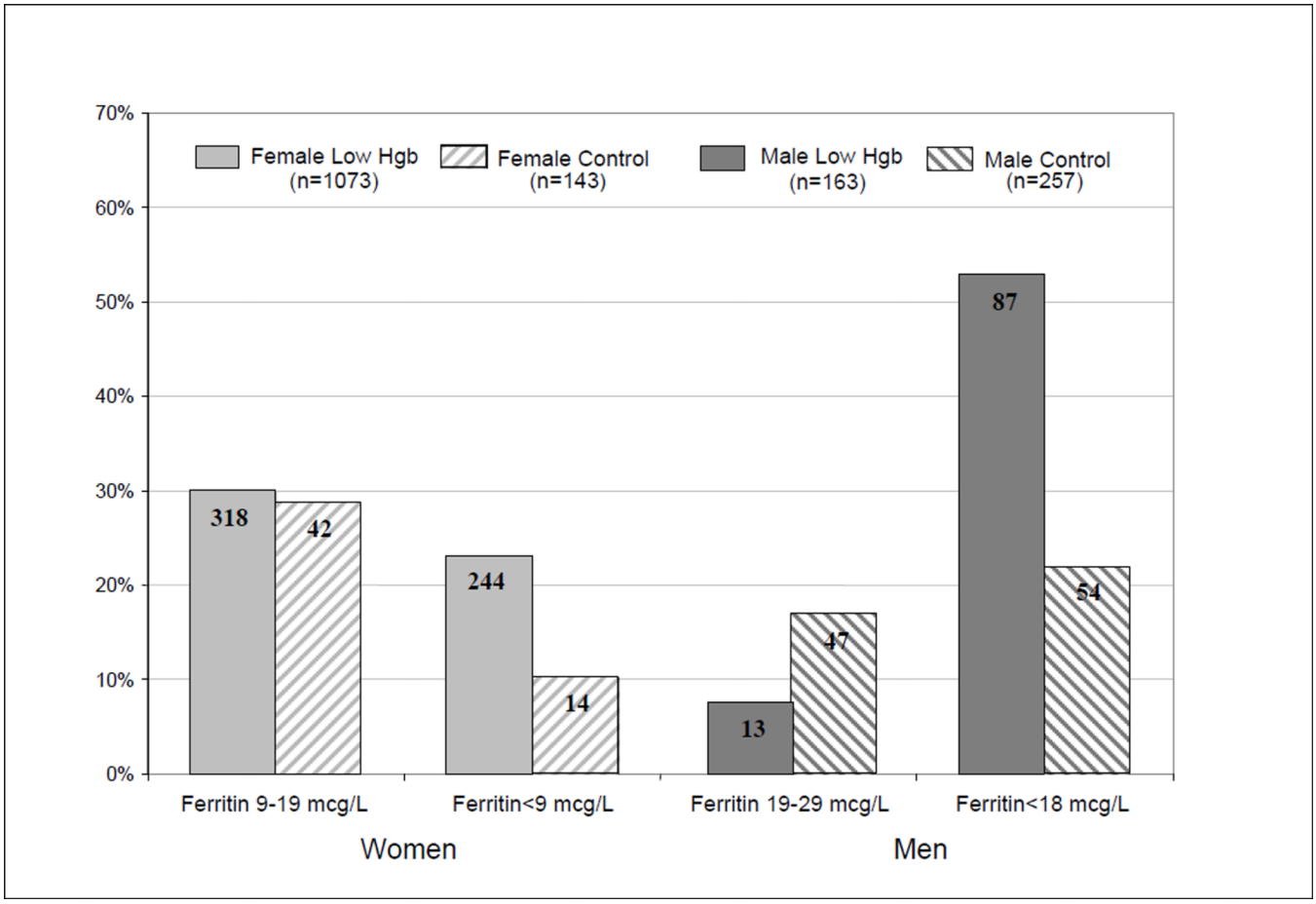

Figure 1.

Percent of donors in the low hemoglobin group and control group who had iron depletion (ferritin between 9–19 mcg/L in women and 19–29 mcg/L in men) and iron deficiency (ferritin <9 mcg/L in women and <18 mcg/L in men). Hgb = hemoglobin.

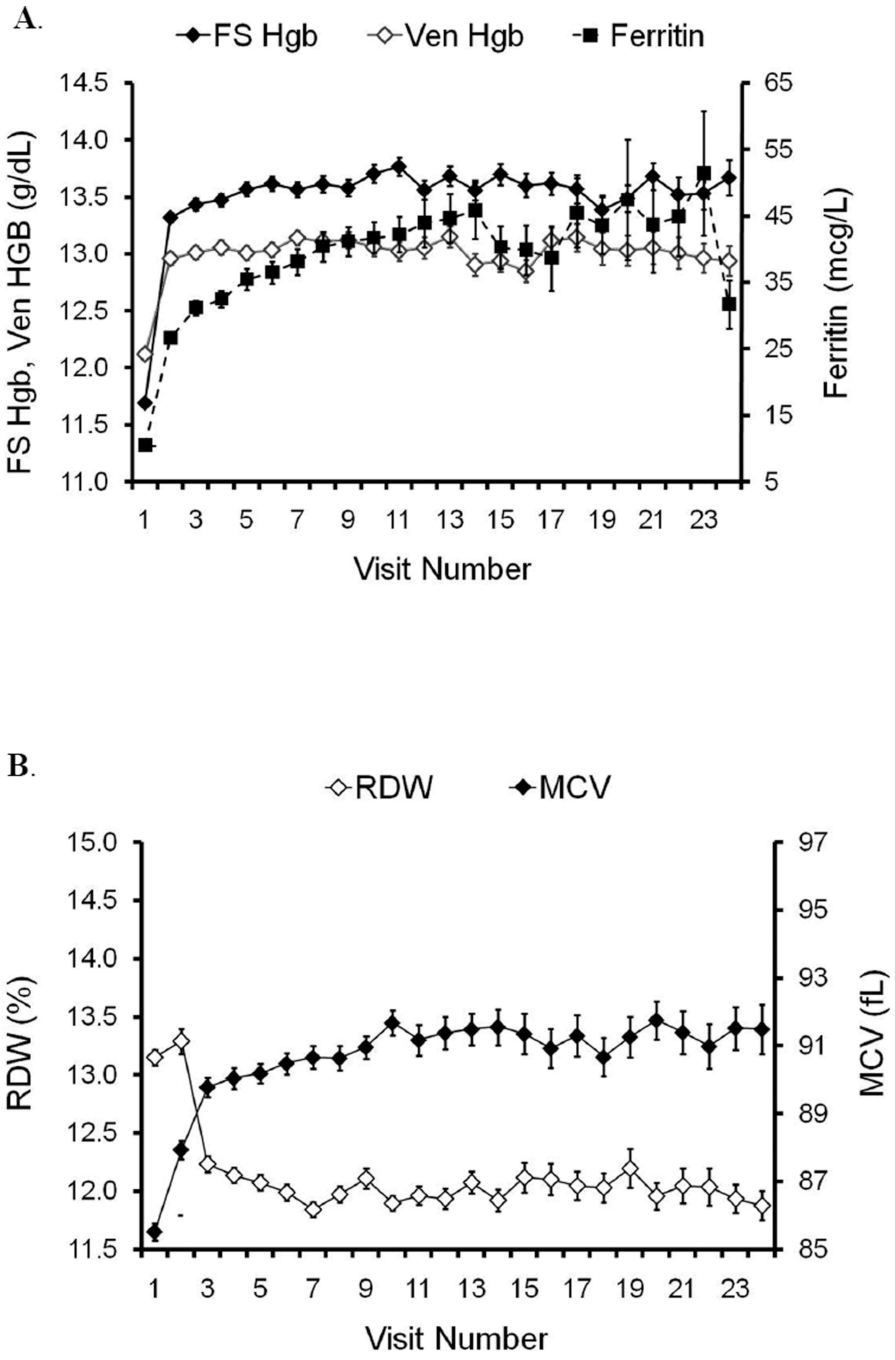

Figure 2.

Effect of iron replacement therapy on (A) fingerstick and venous hemoglobin values and (B) mean corpuscular volume and red cell distribution width, during initial and subsequent visits by donors in the low hemoglobin group. FS = fingerstick, Hgb = hemoglobin, Ven = venous, RDW = red cell distribution width, MCV = mean corpuscular volume.

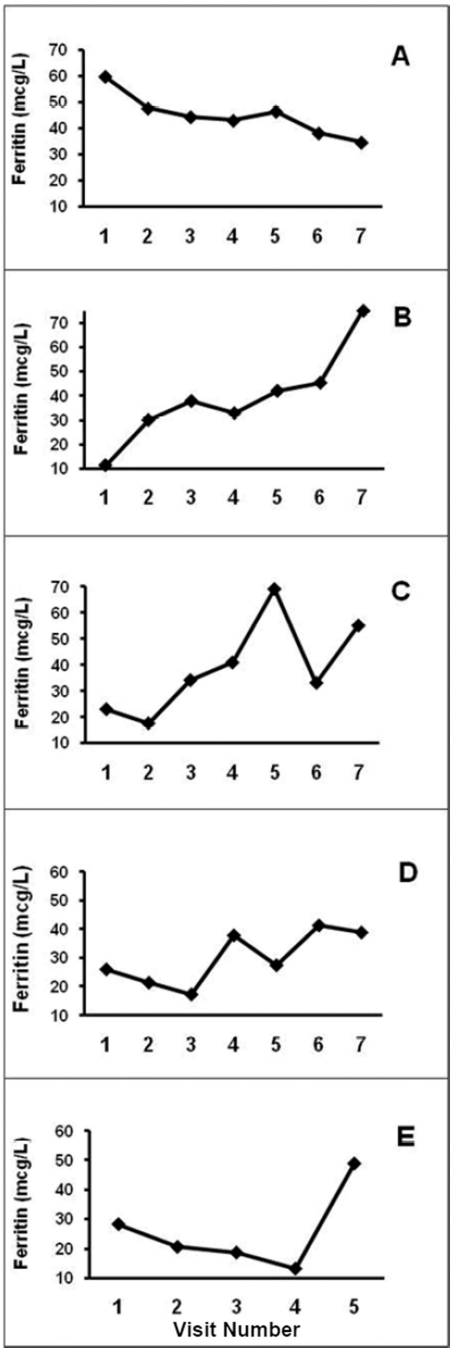

Figure 3.

Ferritin values on initial and subsequent visits in donors in the control group. Donors in this group were given iron replacement therapy only if they demonstrated iron deficiency (ferritin <9 mcg/L in women or <18 mcg/L in men). (A) In donors who were not placed on iron replacement therapy, ferritin levels decreased with each additional donation. In donors started on iron replacement therapy after their (B) first visit, (C) second visit, (D) third visit, or (E) fourth visit, ferritin levels declined until the specific visit on which iron replacement was initiated, at which point ferritin values increased even as the donors continued to donate blood.

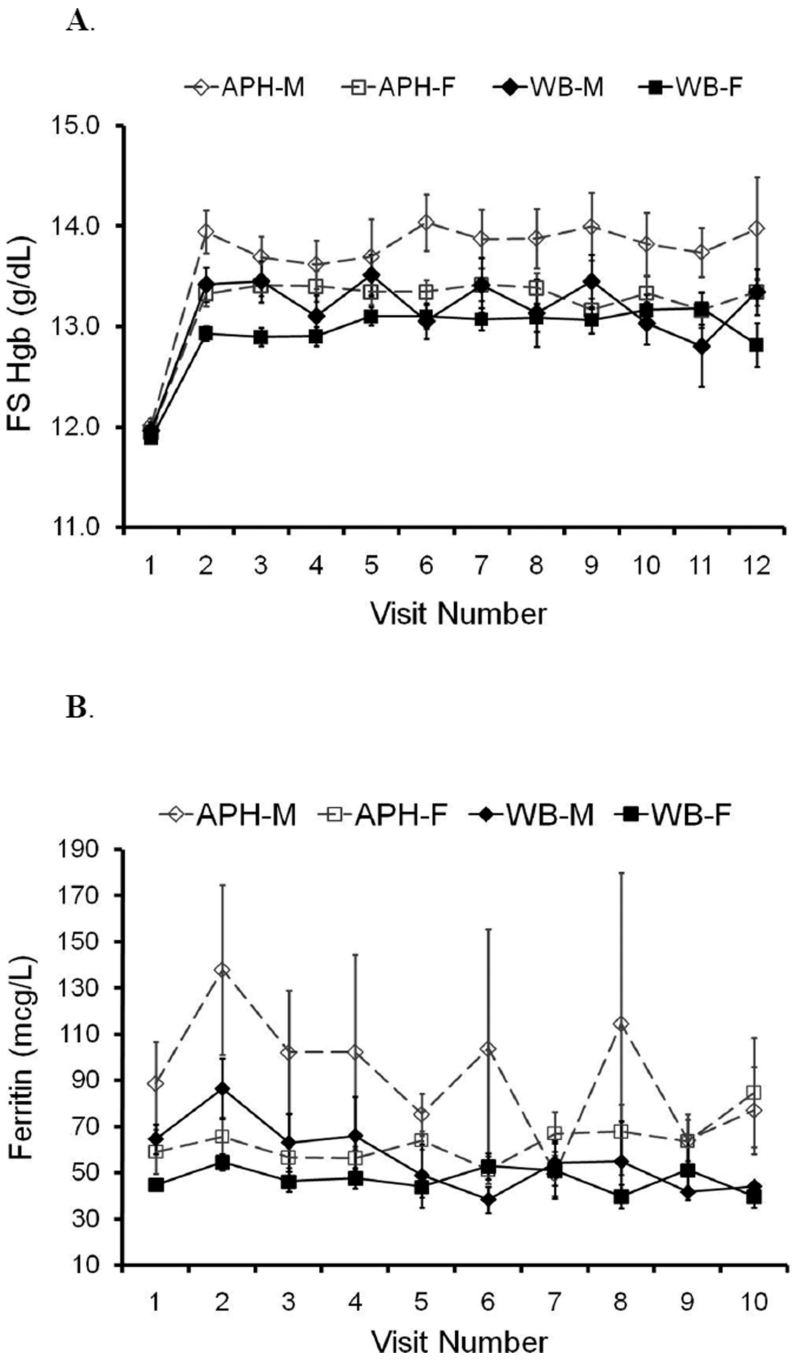

Figure 4.

Effect of iron replacement therapy in donors deferred for a low fingerstick hemoglobin who did not have iron depletion or deficiency on initial visit. (A) Fingerstick hemoglobin values on initial and subsequent visits. (B) Ferritin values on initial and subsequent visits. APH-M = male apheresis donors, APH-F = female apheresis donors, WB-M = male whole blood donors, WB-F = female whole blood donors, FS = fingerstick, Hgb = hemoglobin.

Table 1

Donor Demographics at Study Enrollment

			Low Hgb Group (n= 1236)	Control Group (n = 400)	p value
Females	Number of donors		1073 (89%)	143 (37%)	<0.0001
	Age (range)		39 (17–82)	46 (23–69)	<0.0001
Males	Number of donors		163 (11%)	257 (63%)	<0.0001
	Age (range)		53 (22–85)	49 (18–80)	0.0005
Race	Caucasian		832 (65%)	331 (80%)	<0.0001
	African American		215 (19%)	21 (6%)	<0.0001
	Asian		76 (7%)	31 (9%)	0.1370
	Hispanic		51 (4%)	7 (2%)	0.0403
	Other		62 (5%)	10 (3%)	0.0275
First Time Donors	Number of donors		376 (37%)	46 (16%)	<0.0001
# Prior Donations	Females	WB (range)	10.1 (1–103)	16.0 (1–103)	0.0065
	Males	WB (range)	26.5 (1–172)	25.7 (1–185)	0.7185

Hgb = hemoglobin. WB = whole blood.

Table 2

Association of FS Hgb Levels with Iron Status and Venous Hgb in Women

Women (n=1216)	Fingerstick Hemoglobin Levels (g/dL)			
	<11.5	11.5–11.9	12.0–12.4	≥12.5
Iron Status	**(n=256)**	**(n=302)**	**(n=515)**	**(n=143)**
Iron deficient	40% (102) * 4%	24% (72) 4%	14% (70) 1%	10% (14) 3%
Iron depleted	26% (66) 5%	28% (86) 4%	32% (166) 5%	29% (42) 7%
Iron replete	34% (88) 6%	48% (144) 11%	54% (279) 13%	61% (87) 24%
Venous Hgb ≥ 12.5	18% (47) **	35% (106)	55% (283)	80% (115)

FS=fingerstick, Hgb=hemoglobin

* Data shown as percent (number) of donors in each fingerstick hemoglobin column who were iron deficient, depleted, or replete. Second percent refers to portion of donors in each column who were menopausal.

** Data shown as a percent (number) of donors in each fingerstick hemoglobin column who had venous hemoglobin levels ≥ 12.5 g/dL.

Table 3

Association of FS Hgb Levels with Iron Status and Venous Hgb in Men

Men (n=420)	Fingerstick Hemoglobin Levels (g/dL)				
	<12.0	12.0–12.4	12.5–12.9	13.0–13.4	≥13.5
Iron Status	**(n=74)**	**(n=89)**	**(n=9)**	**(n=19)**	**(n=229)**
Iron deficient	62% (46) *	46% (41)	56% (5)	26% (5)	19% (44)
Iron depleted	6% (4)	10% (9)	22% (2)	26% (5)	18% (40)
Iron replete	32% (24)	44% (39)	22% (2)	48% (9)	63% (145)
Venous Hgb ≥ 12.5	55% (41) **	69% (61)	78% (7)	95% (18)	100% (229)

FS=fingerstick, Hgb=hemoglobin

* Data shown as percent (number) of donors in each fingerstick hemoglobin column who were iron deficient, depleted, or replete.

** Data shown as a percent (number) of donors in each fingerstick hemoglobin column who had venous hemoglobin levels ≥ 12.5 g/dL.

Table 4

Adverse Events during Iron Replacement Therapy

	Number of Donors Developing Intolerance to Iron with First Prescription (n = 405 of 1362)					
	Ferrous Sulfate n = 278* of 1084			Ferrous Gluconate n = 127 of 278		
Symptom Severity	**Severe****	**Moderate**	**Mild**	**Severe**	**Moderate**	**Mild**
Constipation	37	72	51	33	40	13
Abdominal Cramping	16	18	4	5	6	2
Diarrhea	8	8	4	2	3	2
Nausea	2	15	11	2	5	2
Vomiting	4	1	0	1	0	0
Bloating/Indigestion	3	10	2	2	5	0
Headache	1	1	0	1	0	0
Metallic Taste/Sore Mouth	1	3	0	1	1	0
Pruritis/ Rash/Hives	1	3	0	0	0	0
Other***	1	2	0	0	1	0

* One donor reported 2 symptoms of intolerance.

** Symptom severity grades of severe, moderate, and mild were based on self-reports by donors.

*** Includes 1 each: flushing, foul smelling urine, leg cramps, hyperactive bowel sounds