ASSOCIATION BULLETIN

#12-03

Date: September 21, 2012
To: AABB Members
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Re: Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors

This bulletin, developed by the AABB Interorganizational Task Force on Donor Hemoglobin Deferrals, contains information and recommendations for all establishments that collect whole blood from donors. It provides updated information about and recommendations of action(s) to monitor, limit, or prevent iron deficiency in blood donors.

Summary
AABB recommends that blood collecting organizations provide donors with information on the risks of postdonation iron deficiency. Further, blood collecting organizations should take action(s) to monitor, limit, or prevent iron deficiency in blood donors. Actions, which may be directed toward all donors or selectively to donor subpopulations, may include: measurement of serum or plasma ferritin, blood center programs to provide replacement iron, recommendations to donors to take over-the-counter iron supplements, and lengthening of the interdonation interval or restriction of the number of donations in a 12-month period.

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Background
Although there have been previous reports of iron depletion, iron deficiency anemia, and iron replacement in blood donors,¹⁻⁵ this issue has received heightened attention in the past year. A National Institutes of Health (NIH)-funded group of blood centers (REDS-II) conducted the REDS-II Donor Iron Status Evaluation (RISE) study, which provided a significant amount of data documenting the current extent of this problem.⁶⁻⁸

The RISE study looked at two donor cohorts: 1) first-time and reactivated donors (no whole blood or red cell donations in the prior two years), a cohort composed of males and females with iron stores not affected by blood donation, and 2) frequent donors (females with two or more and males with three or more whole blood or red cell donations in the year prior to their enrollment donation). Donors were encouraged to donate frequently for 15 to 24 months. At the final study
visit, the prevalence of iron-deficient erythropoiesis (IDE) and absent iron stores (AIS) were 51% and 20%, respectively, for females and 20% and 8%, respectively, for male donors in the first cohort. For donors in the second cohort, the prevalence of IDE and AIS were 62% and 27%, respectively, for females and 47% and 18%, respectively, for males at the final study visit. This study demonstrated a high prevalence of iron deficiency and depletion in frequent blood donors. The self-reported use of over-the-counter iron supplements or multivitamins containing iron was associated with a decreased risk of IDE and AIS, suggesting that the use of iron replacement in blood donors may allow more frequent donations without the depletion of iron. Other RISE study results suggested that increasing the interdonation interval or restricting the number of allowable donations per 12-month period may reduce the prevalence of both IDE and AIS and reduce hemoglobin (Hb) deferral rates. RISE investigators suggested that both these approaches should be further evaluated as separate and/or combined initiatives.

After a Food and Drug Administration (FDA) Blood Products Advisory Committee meeting considered the Hb standards for donation and iron loss in blood donors, the FDA Center for Biologics Evaluation and Research organized a workshop called Hemoglobin Standards and Maintaining Adequate Iron Stores in Blood Donors on November 8 and 9, 2011. At this workshop, co-sponsored by the National Heart, Lung, and Blood Institute, Plasma Protein Therapeutics Association, AABB, America’s Blood Centers, and the Office of the Assistant Secretary of Health, experts presented and extensively discussed this topic.

No specific recommendations emerged from the workshop or from the most recent publications, but there was a clear focus on the impact of blood donation on body iron stores and its disproportionate effect on the health of menstruating women. The iron loss from blood donation combined with the iron loss from menses results in a high likelihood of iron deficiency, often leading to iron deficiency anemia. Older women and men who donate frequently are also susceptible. Clearly, iron deficiency anemia is the greatest concern but iron deficiency in the absence of anemia is also increasingly being recognized as a problem. Depending on the degree of anemia, donors may experience fatigue, which can result in an extensive medical evaluation. Although information is conflicting, cognitive changes, reduced functional capacity, pica, and restless leg syndrome have been described in non-anemic iron-deficient individuals. Previous hypotheses regarding benefits of reduced iron stores (lower cardiac disease risk) have not been substantiated.

Recommendations
Blood establishments should move forward with actions to reduce the risk of iron deficiency in donors. Although current information may be insufficient to immediately require a change in donor eligibility standards, other actions can help ensure the continued safety of blood donation.

Blood collecting organizations should provide their donors with helpful and useful information on the risks of postdonation iron deficiency in menstruating women and in all donors after frequent donation. Adverse effects, risks, and consequences of iron deficiency should be listed and discussed as well as information on maintaining iron balance by taking iron supplements. This information should also be integrated with the blood donation consent process. America’s Blood Centers is currently developing predonation information for blood donors, called the Written Statement of Understanding, to help educate donors about possible
risks associated with donating blood as well as what to expect during the donation process and after donating. The goals of this education recommendation can also be met by use of the predonation information document for blood donors (Attachment 1) on iron deficiency and maintaining iron balance, developed by the AABB Task Force.

One or more of the following actions should be taken, either in all donors, or in selected donor populations at greatest risk for iron depletion.

1. Measurement of serum or plasma ferritin

Serum or plasma ferritin is currently the single best test for monitoring donor iron status; however, it cannot be performed at the time of blood collection. A serum ferritin level below 12 ng/dL has excellent specificity but poor sensitivity for iron deficiency. A serum ferritin level of 26 ng/dL as an iron status decision point has slightly reduced specificity but much improved sensitivity for iron deficiency. Ferritin testing might be useful for all whole blood and red cell donors or it could be used selectively for certain donor subpopulations such as menstruating females, frequent donors (males with three or more donations or females with two or more donations within the past 12 months), or young donors (eg, 16- to 18-year-olds). The ferritin measurements could be used to assist the donor in regulating their frequency of donation to maintain iron stores, could be used as a donor eligibility criterion by the blood center, or could serve as a triage criterion for offering donors iron replacement.

In 2004, routine serum ferritin testing of blood donors was implemented at The Blood Transfusion Center, Swiss Red Cross, Basel, Switzerland. The investigators concluded that serum ferritin measurements combined with a set of actions that donors could pursue allowed for optimal management of iron deficiency and was effective in preventing iron deficiency anemia in their donors.

2. Iron replacement to prevent iron depletion, either in the form of medication provided by the blood center or specific instructions to the donor on use of over-the-counter iron supplements

In the United States, only two facilities, the NIH Clinical Center and the Indiana Blood Center, are known to currently provide oral iron tablets to selected donor subpopulations. A conservative iron replacement program could specifically target donor populations such as menstruating females, young donors, or frequent donors with the goal of replacing the amount of iron lost from a whole blood donation during the current 56-day minimum interdonation interval. By limiting the total dose of elemental iron replaced to approximately 2 grams, iron lost during the prior donation can be maximally replenished while minimizing the adverse effects of such replacement therapy. When the strategy is limited to replacement of iron lost during donation, the risk of masking colon cancer or worsening hemochromatosis is minimized. The use of carbonyl iron preparations (in child-proof bottles) has a lower toxicity profile than ferrous iron and also diminishes the risk of accidental overdose in children.
The results of an iron replacement program for blood donors at the NIH Clinical Center (Bethesda, MD) have been published recently. Over 39 months, 1236 blood donors deferred for a low Hb and 400 non-deferred donors were evaluated for iron depletion and deficiency (as defined by serum ferritin levels). Among the donors deferred for low Hb, iron depletion or deficiency was found in 53% of females and 61% of males. In the non-deferred donors, iron depletion or deficiency was found in 39% of females and 39% of males. Donors deferred for low Hb and non-deferred donors with serum ferritin levels below the lower limit of the reference range were given a 60 pack of 325 mg oral ferrous sulfate tablets (65 mg of elemental iron) with instructions to take one tablet daily. After iron replacement therapy, iron-related laboratory parameters normalized in all donors, even in the face of continued blood donations. It was concluded that routine iron replacement in blood donors was a safe and effective approach for the prevention of iron depletion and deficiency. An additional study of iron replacement in female blood donors < 50 years old with iron deficiency without anemia showed that four weeks of oral ferrous sulfate, 80 mg of elemental iron/day, resulted in a significantly lower prevalence of a ferritin level < 12 ng/mL compared to donors given placebo.

3. Prolonging the interdonation interval or restricting the total number of allowable donations in a 12-month period for whole blood and red cell donations

If this approach is adopted, a consideration is its potential impact on the blood supply. A recent publication and data from the American Red Cross Blood Services show that lengthening the interdonation intervals to 12 or 16 weeks with no other attendant changes in donor qualification (ie, minimum acceptable Hb level) would have a significant deleterious impact on the blood supply. In addition to general supply shortages, there may also be selective shortages of O negative or rare phenotype red cells. Lengthening the interdonation interval or restricting the total number of donations in a 12-month period do hold the promise of decreasing the risk of iron depletion in blood donors by allowing more time for iron recovery, but they are interventions that will require carefully planned implementation along with additional strategies in order to minimize a negative impact on the blood supply.

As a word of caution, if Hb levels are used to assess the success of these approaches, there needs to be a clear understanding that Hb is a poor indicator of underlying iron status. More accurate measures of iron status, such as serum or plasma ferritin, are preferable for monitoring the success of such programs.

Postimplementation Considerations
Organizations are encouraged to collect, track, tabulate, and report data on any interventions they conduct. AABB also strongly encourages organizations planning to evaluate new donor iron management strategies to design their interventions in such a way that endpoints are clear and the data derived can be readily compared to interventions implemented at other blood collection facilities. Particularly important are any impacts on blood availability, iron status of donors, and deferrals due to low Hb.

Further information to guide policy to prevent iron depletion should be forthcoming in the next two to three years from two NIH-supported studies. STRIDE (STrategies to Reduce Iron
DEficiency) is being conducted in three geographic areas with five study arms (standard care, ferritin measurement plus education, and iron replacement using two different iron doses and a placebo). HEIRS (HEmoglobin Iron Recovery Study) is being conducted by the REDS-III group in several geographic areas to compare postdonation donor Hb recovery in donors with and without iron replacement.

The use of techniques to prevent iron depletion in blood donors might allow for the minimum Hb acceptance criteria in females to be decreased to a more physiologic cutoff (e.g., 12.0 g/dL) without worsening the already significant risk of iron depletion in this donor population. This would allow for the qualification of more iron-replete female donors who currently do not meet Hb acceptance criteria. This could enhance the blood supply, increase female donor satisfaction, and decrease the number of unnecessary medical evaluations in female donors who currently have borderline low Hb levels. Blood centers considering the option of lowering the minimum Hb acceptance criteria in females are advised that such a practice does not conform to current FDA regulations or AABB standards. The regulatory department at AABB (Regulatory@aabb.org) is available to assist organizations in determining the steps required to implement such a practice change. FDA representatives have indicated that while a “one size fits all” variance template is not appropriate, they would be interested to engage in discussion with collection organizations that are contemplating approaches that may require an exception or alternative procedure allowed under 21 CFR 640.120.

References


Thank you for coming to donate blood.

We care about your health and want you to know that donating blood reduces iron stores in your body. In many people, this has no effect on their health. However, in some people, particularly younger women and frequent donors of either gender, blood donation may remove most of the body’s iron stores. We want you to understand these issues more clearly.

What happens to me during a blood donation?
Red blood cells are red because of the way iron is carried in hemoglobin, a protein that brings oxygen to the body. Therefore, the removal of red blood cells during blood donation also removes iron from your body. The impact of this iron loss on your health varies among donors.

How does blood donation affect iron stored in my body?
Iron is needed to make new red blood cells to replace those you lose from donation. To make new red blood cells, your body either uses iron already stored in your body or uses iron that is in the food you eat. Many women have only a small amount of iron stored in their body, which is not enough to replace the red blood cells lost from even a single donation. Men have more iron stored in their body. However, men who donate blood often (more than two times per year) may also have low iron stores.

Does the blood center test for low iron stores in my body?
No, the blood center tests your hemoglobin but not your iron stores. Hemoglobin is a very poor predictor of iron stores. You may have a normal amount of hemoglobin and be allowed to donate blood even though your body’s iron stores are low.

How may low iron stores affect me?
There are several possible symptoms associated with low iron stores. These include fatigue, decreased exercise capacity, and pica (a craving to chew things such as ice or chalk). In addition, having low iron stores may increase the possibility of having a low hemoglobin test, preventing blood donation.

What can I do to maintain my iron stores?
While eating a well-balanced diet is important for all donors, simply eating iron-rich foods may not replace all the iron lost from blood donation. Taking multivitamins with iron or iron supplements either prescribed or over the counter (from a drugstore) may help replace iron lost. Iron supplements vary in name and proportion of iron within the tablet/caplet. The most effective dose, type of iron supplement, and length of treatment are currently being studied. Current recommendations range from one typical multivitamin with iron (19 mg iron) to elemental iron caplets (45 mg iron) for six weeks to three months. Your physician or pharmacist may be able to assist you in deciding what dose, type, and duration of iron supplement to choose.

Why doesn’t a single big dose of iron replace what I lose during the donation?
Because people have a limit in iron absorption (ie, 2-4 mg/day), taking iron in larger doses for a shorter period may not lead to better absorption (and may result in more side effects). The overall goal is to replace, over 1 to 3 months, 200-250 mg of iron lost during donation.

Where can I get additional information?
Individual blood centers should complete this paragraph. They may wish to refer donors to a local expert, or a local website. There are also established internet sites with expertise that may be helpful for donors, including www.anemia.org