Advancing Transfusion and Cellular Therapies Worldwide

Management of Risk for Iron Deficiency In Female Blood Donors with HB levels of 12.0 - <12.5 g/dL

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The Donor Eligibility Final Rule:

- "Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use"
- Published May 2015
- Effective date: May 23, 2016

As described in the preamble of the Final Rule:

- Following the review of data presented at the July 2010 Blood Products Advisory Committee meeting, the members voted unanimously in support of raising the hemoglobin (HB) level for men, but did not support a change in the HB level for women.
- The issue was also addressed at the November 2011 "Public Workshop: Hemoglobin Standards and Maintaining Adequate Iron Stores in Blood Donors Presentations."
- Data from numerous studies, as referenced in the final rule, were considered.

Based on the data in those studies, FDA decided:

- To promulgate different standards for male and female donors based on BPAC discussions and the “Public Workshop: Hemoglobin Standards and Maintaining Adequate Iron Stores in Blood Donors Presentations”.
  - Revising the requirement for males donors from 12.5g/dL to 13.0 g/dL.
  - Retaining the 12.5 g/dL HB minimum for female donors.

The Final Rule:

- Acknowledged that HB levels between 12.0 and 12.5 g/dL are within the “normal range” for women.
- The new regulation at 21 CFR 630.10(f)(3)(i)(A)
  - Provides the option to develop an alternative standard
  - Differs from a “request for a variance” under 21 CFR 640.120.

The new regulations at §630.10(f)(3)(i)(A) regarding the option for this alternative standard:

- Authorize blood collection "from female allogeneic donors who have a hemoglobin level between 12.0 and 12.5 grams per deciliter…"

Provided that-

- "You [the establishment] have taken additional steps to assure that this alternative standard is adequate to ensure that the health of the donor will not be adversely affected due to the donation…"
- Your procedure "has been found acceptable for this purpose by FDA."

AABB FDA Liaison Meeting
September 21, 2015

- FDA's Final Rule did not address minimum elements that should be included in standard operating procedures (SOPS), as several related studies concerning ferritin testing and iron supplementation were still ongoing at the time.
- The Liaison Committee discussed the goal of reaching an understanding regarding the minimum elements that would be acceptable to the FDA.
- At the time of this meeting, FDA had not yet received a submission for approval of an alternative standard.

AABB FDA Liaison Meeting
September 21, 2015

- AABB suggested the formation of a working group with FDA liaisons.
- FDA representatives agreed that the output of a working group could help the process for blood establishments that choose to prepare a submission for FDA approval.
- The working group was charged with exploring acceptable elements aimed at ensuring the health of female donors with HB levels as low as 12.0 g/dL.
- Minimal elements are intended to provide blood establishments adequate flexibility to develop and implement programs that work best in their own environment.

Following the September 2015 AABB FDA Liaison Committee meeting:

- AABB asked member experts to join the Work Group on Management of Female Hemoglobin Levels (the Working Group).
- The Working Group was tasked with:
  - Reviewing current literature and relevant experience with this issue.
  - Identifying a range of strategies to assist blood collection establishments who elect to develop this alternative standard
  - Providing flexible strategies that:
    - Incorporate minimal elements of an acceptable approach.
    - Can be refined to meet the unique operational needs and preferred approach of individual blood collection establishments.
- AABB's Donor Health and Safety Committee reviewed the templates as developed by the Working Group.

As noted on each template and the Q&A tool, the strategies developed by the Working Group *have not been approved by the FDA*;

A blood collection establishment that elects to collect from this group of female donors must first:

1. Develop SOPs, based on these strategies or other protocols they develop;
2. Submit those SOPs to FDA in a prior approval supplement.

The final product of the Working Group was posted on AABB's website

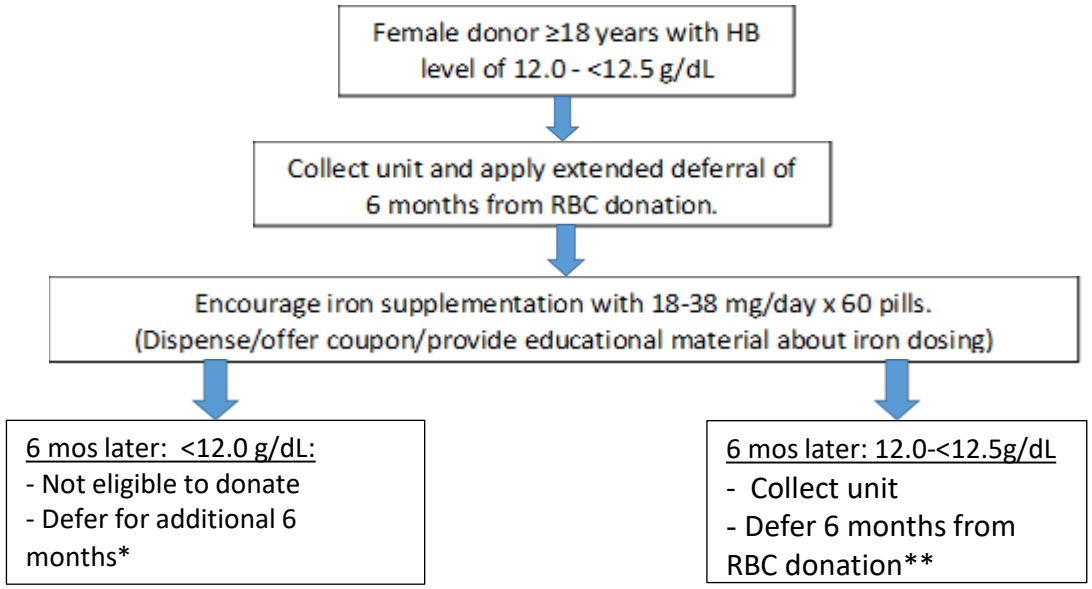
Consistent with the goal for creating flexible strategies, templates for two approaches were posted:

1. Management of risk for iron deficiency in these female blood donors **using extended deferral *without* ferritin testing.**
2. Management of risk for iron deficiency in these female blood donors **using ferritin testing.**

Templates include a Q&A with References and Data to assist individual blood collection establishments in refining an approach and can be found on the AABB website:

http://*www.aabb.org/advocacy/regulatorygovernment/donoreligibility/hsim/Pages/Management-of-Risk-for-Iron-Deficiency-in%20Female-Blood-Donors-with-HB-Levels-12.0-12.5.aspx*

Donor Management - Extended Deferral Without Ferritin Testing:



* A blood establishment may consider a shorter deferral period if the donor is 1) further evaluated by the blood center, including evaluation of adequate donor compliance with an iron supplementation regimen, whether the iron supplement is provided by the blood establishment or procured by the donor on her own, or 2) the donor is referred for evaluation.

**A blood establishment may defer for 56 days or longer from RBC donation contingent on the blood establishment evaluation of adequate donor compliance with an iron supplementation regimen, whether the iron supplement is provided by the blood establishment or procured by the donor on her own.

Q & A for use with EXTENDED DEFERRAL *WITHOUT* FERRITIN TESTING:

Q: Why is 6 months the suggested deferral period in the "No Ferritin Testing" algorithm?

A: The REDS-III HEIRS Study showed that for donors not taking iron, on average the recovery to pre-donation ferritin levels took longer than the 168-day follow-up. Recovery of hemoglobin was highly variable and 2.5 to 5 times longer on average for donors not taking iron, compared to those randomized to take iron, who recovered in a month.

Q: Why is the recommended dosing for iron supplements 18-38 mg/day?

A: The REDS-III HEIRS study used 38 mg/day, and the STRIDE Study found equivalent efficacy of 19 and 38 mg/day doses in protecting against iron deficiency.

Multivitamins with iron might have 18 mg in them and separate iron supplements might have about 38 mg elemental iron.

Q: Why suggest iron supplements for only 8 weeks, isn't longer better?

A: Donors randomized to take iron in the REDS-III HEIRS study took 38 mg of iron daily for 24 weeks of observation, and the investigators found that nearly 90% of the benefit of taking iron occurred during the first 8 weeks. It is assumed that donor compliance might be higher if the period for which they are asked to take iron is shorter, but that was not assessed in the study.

Q: Isn't a shorter deferral period between donations acceptable if the donors take iron?

A: HEIRS found that while hemoglobin recovery was estimated to occur within the current interdonation interval for those taking iron, recovery of ferritin was slower (median of 76 days).

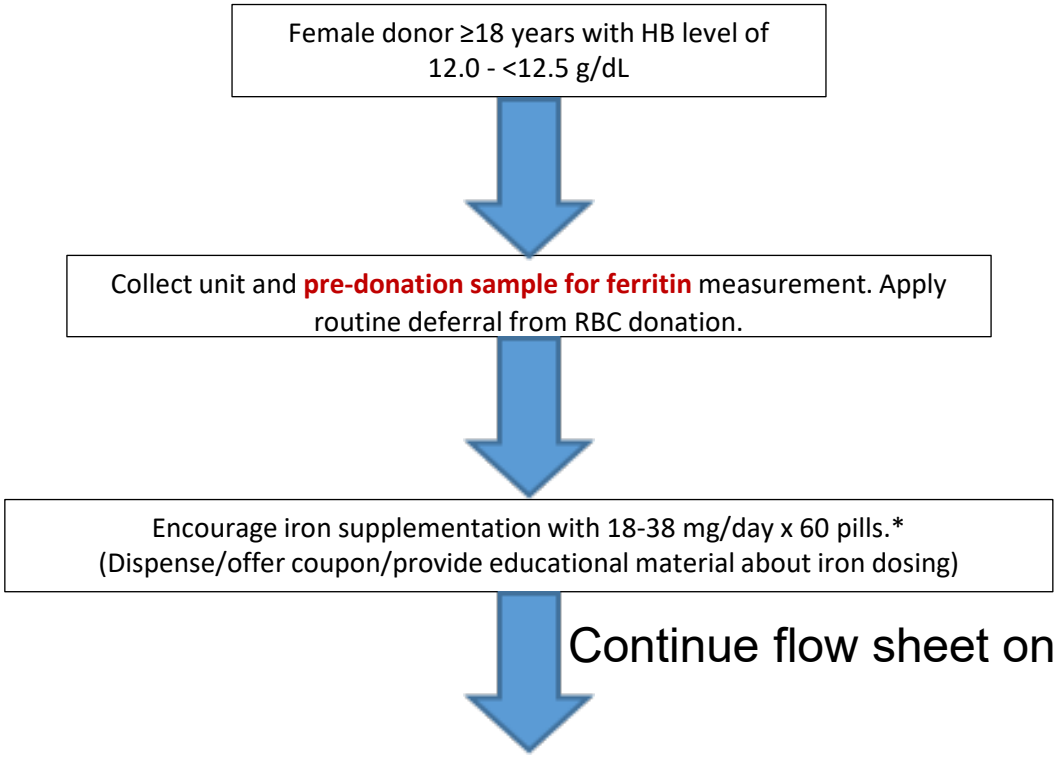
In STRIDE, those assigned to 19 or 38 mg of iron daily reduced their odds of ferritin < 26 or < 12 ng/mL by 80% but did not reduce those odds to zero; e.g., at the end of the study, more than 30% of those taking iron had ferritin < 26 ng/mL.

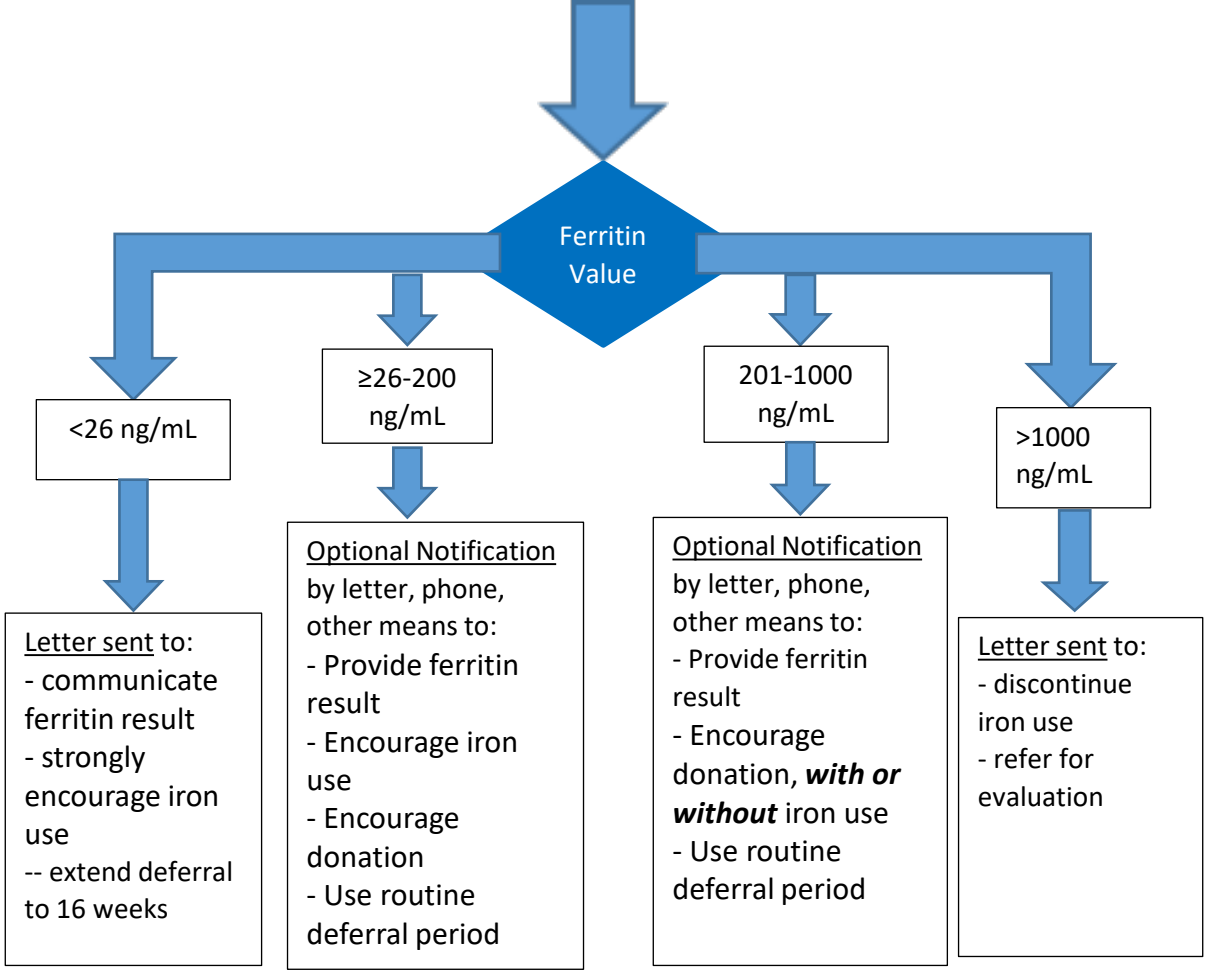
Encouragement of iron consumption for female donors does not ensure compliance (and it is anticipated that some donors will choose not to take iron), the tracking of which could be operationally cumbersome.

A 6-month deferral in the absence of ferritin monitoring accommodates the variable and often lengthy recovery periods for hemoglobin and ferritin for many donors.

For centers that choose to evaluate donor compliance with an iron supplementation regimen, a deferral period shorter than 6 months may be worked into the protocol at an appropriate stage.

Donor Management - Ferritin Testing





This flow sheet suggests options for encouraging iron supplementation (18-38 mg/day x 60 pills)* with exceptions noted. Suggestions include dispensing iron, offering coupons, and providing educational material about iron supplementation.

*Exceptions noted for ferritin 200 ng/ml or greater

Q & A for use *WITH* FERRITIN TESTING:

Q: Why is 16 weeks the suggested deferral period for women with a ferritin level < 26 g/dL in the "Ferritin Testing" algorithm?

A: The REDS-III HEIRS Study found that while hemoglobin recovery was estimated to occur within the current interdonation interval for those taking iron, recovery of ferritin was slower (median of 76 days).

Some of the female donors with ferritin < 26 ng/mL will have absent iron stores (indicated by a ferritin level < 12 ng/mL). The goal would be to replete them beyond their pre-donation level, optimally to > 26 ng/ml.

A longer interval than the current 8-week donation interval would be indicated for that.

The assumption is that many donors receiving a letter reporting their low ferritin results would, in fact, be responsive to the message and either delay their next donation or purchase and take iron, or both. STRIDE found that 70% of donors receiving such a letter responded with one or both measures.

Q: Isn't a shorter deferral period between donations acceptable if the donors take iron?

A: HEIRS found that while hemoglobin recovery was estimated to occur within the current interdonation interval for those taking iron, recovery of ferritin was slower (median of 76 days).

In STRIDE, those assigned to 19 or 38 mg of iron daily reduced their odds of a ferritin level < 26 or < 12 ng/mL by 80% but did not reduce those odds to zero.

At the end of the study, more than 30% of those taking iron had a ferritin level < 26 ng/mL. *Encouragement of iron consumption for female donors does not ensure compliance, the tracking of which could be operationally cumbersome*.

Q: What proportion of female donors should I expect to have a ferritin level < 26 ng/ml?

A: Based on the REDS-II RISE study, simulations using REDS-II donation data and RISE data and unpublished data from Blood Systems Incorporated, blood establishments might expect half or more of their female donors with Hb < 12.5 g/dL to have a ferritin level < 26 ng/ml.

Q: Above what ferritin level should donors be advised to stop taking iron supplements?

A: Some donors with a high enough ferritin level will not need to take iron supplements. It is up to the blood establishment's medical director to determine at what ferritin level a donor is no longer encouraged to take iron supplements. That level might vary according to individual donor characteristics, donation behavior and assay used.

References

1. Kiss JE, Brambilla D, Glynn SA, et al. Oral iron supplementation after blood donation: a randomized clinical trial. JAMA 2015;313(6):575-83.

2. Mast AE, Bialkowski W, Bryant BJ, et al. A randomized, blinded, placebo-controlled trial of education and iron supplementation for mitigation of iron deficiency in regular blood donors. Transfusion 2016;56:1588-97. Doi: 10.1111/trf.13469.

3. Cable RG, Brambilla D, et al. Effect of iron supplementation on iron stores and total body iron after whole blood donation. Transfusion 2016; 56(8):2005-12.

4. Cable RG, Bialkowski W, Bryant BJ, et al. Donor behaviors during participation in STRIDE, a randomized, blinded, placebo-controlled trial of education and iron supplementation for mitigation of iron deficiency in regular blood donors. Abstract P6-030A. Abstract Presentations from the AABB Annual Meeting Anaheim, CA, October 24–27, 2015. Transfusion 2015;55:3A-245A. doi: 10.1111/trf.13294.

5. Cable RG, Glynn SA, Kiss JE, et al. Iron deficiency in blood donors: analysis of enrollment data from the REDS-II Donor Iron Status Evaluation (RISE) study. Transfusion 2011;51(3):511-22.

6. Cable RG, Glynn SA, Kiss JE, et al. Iron deficiency in blood donors: the REDS-II Donor Iron Status Evaluation (RISE) study. Transfusion 2012;52:702-11.

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