

Topic 1B: Considerations for blood collections from female donors with hemoglobin levels between 12.0 -12.5 g/dL or hematocrit values between 36-38%

Issue

FDA seeks advice from the Committee on acceptable procedures relevant to the collection of blood and blood components from female donors with hemoglobin levels between 12.0-12.5g/dL or hematocrit values between 36-38%.

Background

FDA has modified blood donor hemoglobin and hematocrit qualification standards over time since 1958. Until recently, FDA required that male and female blood donors have a minimum hemoglobin of 12.5g/dL or hematocrit of 38%. On November 8, 2007, the FDA published in the Federal Register proposed donor eligibility requirements (1). In addition, the FDA solicited comments and supporting data on:

- Changing the acceptable minimum hemoglobin or hematocrit levels for female allogeneic donors from 12.5g/dL or 38% to 12.0g/dL or 36% respectively.
- The possibility of adverse effects if a minimum hemoglobin of 12.0g/dL or hematocrit of 36% is used for females.
- The possibility of adverse effects if a minimum hemoglobin of 12.5g/dL or hematocrit of 38% is used for males.

FDA sought public input on these issues in advisory committee discussions (2) and held a scientific workshop (3). Following these discussions and a review of available scientific studies, FDA published *The Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use* (donor eligibility rule) on May 22, 2015 (4). In the donor eligibility rule, FDA established revisions to the minimum hemoglobin and hematocrit levels required for blood

donations. The rule requires that allogeneic donors must have hemoglobin or hematocrit values that are adequate to assure donor safety and product potency. With these considerations and based on the scientific data available, FDA established the following minimum standards:

- Male allogeneic donors must have a hemoglobin level that is equal to or greater than 13.0 g/dL, or a hematocrit value that is equal to or greater than 39%.
- An autologous donor must have a hemoglobin level no less than 11.0 g/dL, or a hematocrit value no less than 33%.
- Female allogeneic donors must have a hemoglobin level that is equal to or greater than 12.5 g/dL, or a hematocrit value that is equal to or greater than 38%.
- Recognizing that lower levels are also within normal limits for female donors, blood establishments may collect blood from female allogeneic donors who have a hemoglobin level between 12.0 and 12.5g/dL or a hematocrit value between 36 and 38%, provided they 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, in accordance with a procedure that has been found acceptable for this purpose by FDA.

FDA did not define additional steps or acceptable procedures for the collection of blood from female donors with hemoglobin levels between 12.0-12.5g/dL in the regulation. FDA stated in the preamble that procedures or steps to enroll such donors could include a pre-donation measure of iron stores by means of a ferritin test, or iron replacement therapy and monitoring of iron stores (4).

Hemoglobin levels in the United States population

In the United States, the normal range of hemoglobin varies by sex and race.

Beutler et al proposed lower limits of normal for hemoglobin concentration in White and Black males and females (5). The authors used the NHANES III and Scripps – Kaiser Databases, eliminating subjects with iron deficiency anemia by excluding those with transferrin saturation of less than 16% or ferritin level less than 10µg/L. Their suggested lower limits of normal for hemoglobin (hemoglobin below which only 5% of the normal subjects in the population will be found) are in Table 1. The authors suggest that the lower limits of the reference range for hemoglobin in the United States population are 13.7 g/dL in White males, 12.9 g/dL in Black males, 12.2 g/dL in White females, and 11.5 g/dL in Black females. The variation of hemoglobin levels by race is attributable to multiple factors including but not limited to a higher incidence of alpha thalassemia trait in African Americans.

Table 1: Suggested lower limits of normal hemoglobin concentration for White and Black adults in the U.S. (iron deficient subjects were excluded)

Group by age (years)	Hemoglobin, g/dL
White men	
20-59	13.7
60+	13.2
White women	
20-49	12.2
50+	12.2
Black men,	
20-59	12.9
60+	12.7
Black women	
20-49	11.5
50+	11.5

Blood 2006; 107(5) 1747-1750

Concern for iron deficiency in female donors with hemoglobin values between 12.0 and 12.5g/dL

As previously described, the donor eligibility rule published May 22, 2015 provides an alternative standard of hemoglobin or hematocrit levels for female donors with values between 12.0 and 12.5g/dL or hematocrit of 36-38% provided that additional donor protection measures acceptable by FDA are taken.

A key donor safety issue is the incidence of iron deficiency in such donors. This is especially true in premenopausal female donors or donors who have previously donated blood (repeat donors). Studies have identified repeat donations and female gender as risk factors for iron deficiency (6, 7).

The majority of blood donors who present to donate blood are repeat blood donors. In a survey of U.S. whole blood and red blood cell collections in 2013, 32.3% of successful donors were first time donors. The rest were repeat donors who donated an average of 1.6 donations per year (8). Low hemoglobin is a common reason for donor deferral and is strongly associated with female gender (9). Among donors deferred for low hemoglobin, about 40% or more will have hemoglobin levels between 12.0 – 12.4 g/dL (10, 11).

Iron deficiency is a commonly detected reason for low hemoglobin. In a study of donors deferred for low hemoglobin levels, 77% were iron deficient (12). Most of these donors were frequent donors. A Canadian study showed that 90% of female donors (combination of first time and repeat donors) with hemoglobin levels less than 12.5 g/dL had low or absent iron stores (absent- ferritin <12 µg/L, low- ferritin 12 -24 µg/L) compared to 50% in donors with hemoglobin levels greater than 13.0 g/dL, and 67% in donors with hemoglobin levels between 12.5 and 12.9 g/dL (13). Bryant and coworkers also studied iron stores in first time and repeat blood donors. Table 2 summarizes the iron status of the female donors categorized by hemoglobin levels. In the 12.0- 12.4 g/dL group, 46% of the donors were iron deficient (ferritin <

9 µg/L) or iron depleted (ferritin 9 – 19 µg/L) compared to 39% of the > 12.5 g/dL group (14).

Table 2: Association of fingerstick Hb levels with iron status and venous Hb in women

Women (n -1216)	Fingerstick Hb levels (g/dL) <11.5	Fingerstick Hb levels (g/dL) 11.5-11.9	Fingerstick Hb levels (g/dL) 12.0-12.4	Fingerstick Hb levels (g/dL) >12.5
Iron Status (ferritin level)	(n = 256)	(n = 302)	(n = 515)	(n=143)
Iron deficient (< 9 µg/L)	40 (102)* 4	24 (72) 4	14 (70) 1	10 (14) 3
Iron depleted (9-19 µg/L)	26 (66) 5	28 (86) 4	32 (166) 5	29 (42) 7
Iron replete (>19 µg/L)	34 (88) 6	48 (144) 11	54 (279) 13	61 (87) 24
Venous hemoglobin>12.5 g/dL	18 (47)†	35 (106)	55 (283)	80 (115)

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

† Data shown as a percentage (number) of donors in each fingerstick Hb column who had venous Hb levels of at least 12.5 g/dL.

Transfusion. 2012;52(7):1566-1575.

The Australian Red Cross Blood Service examined the impact of different hemoglobin thresholds on iron status. They found that a significant proportion of blood donors were iron deficient (defined as

ferritin <12ug/L) irrespective of the hemoglobin threshold selected (15). Table 3 shows the iron status of 3022 Australian blood donors with different hemoglobin predonation cut off levels at different time periods. In 2004, the threshold was 11.8g/dL for females and changed to 12.0 in 2005. The proportion of iron deficient female donors was lower in the group with the 12.0g/dL threshold .

Table 3: Iron stores in Australian blood donors with different predonation hemoglobin levels

	Total donor population iron deficient (%)
ARCBS Hb threshold from 1/1/04	
Males – 12.6g/dL	6.2
Females – 11.8g/dL	22.0
ARCBS Hb threshold from 1/1/05	
Males – 13.0g/dL	6.0
Females – 12.0g/dL	20.6

ARCBS – Australian Red Cross Blood Service

The current minimum hemoglobin requirement for whole blood collection from female donors in Australia remains at 12.0g/dL. Salvin and coworkers recently studied the ferritin levels of Australian blood donors. Among female donors who had made at least one WB donation in the previous 24 months, iron deficiency was detected in 26.4% compared to 12% in new donors, and increased with donation frequency (16).

AABB proposed procedure for collection of blood from female donors with hemoglobin values between 12.0-12.5g/dL

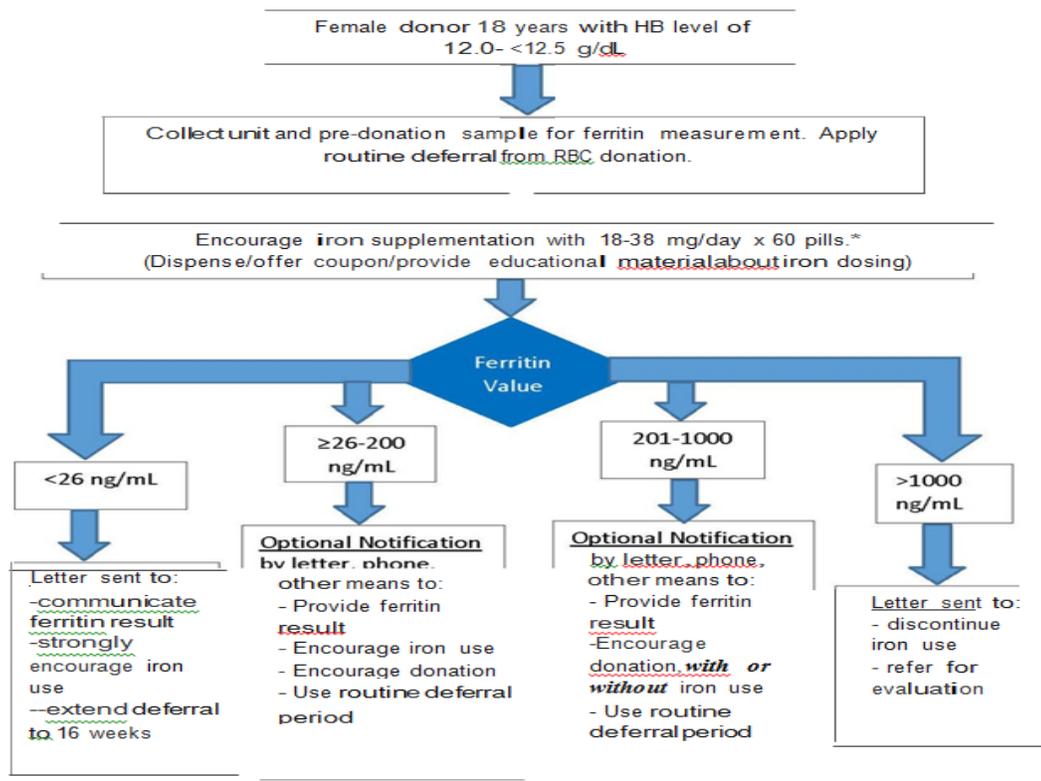
The AABB formed a workgroup to develop flow sheets containing proposed strategies that blood establishments could use to develop procedures for FDA review. The workgroup explored available scientific data, experiences in blood

centers, and considerations of operational impact during development of the flow sheets. AABB has published two flow sheets on their 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>

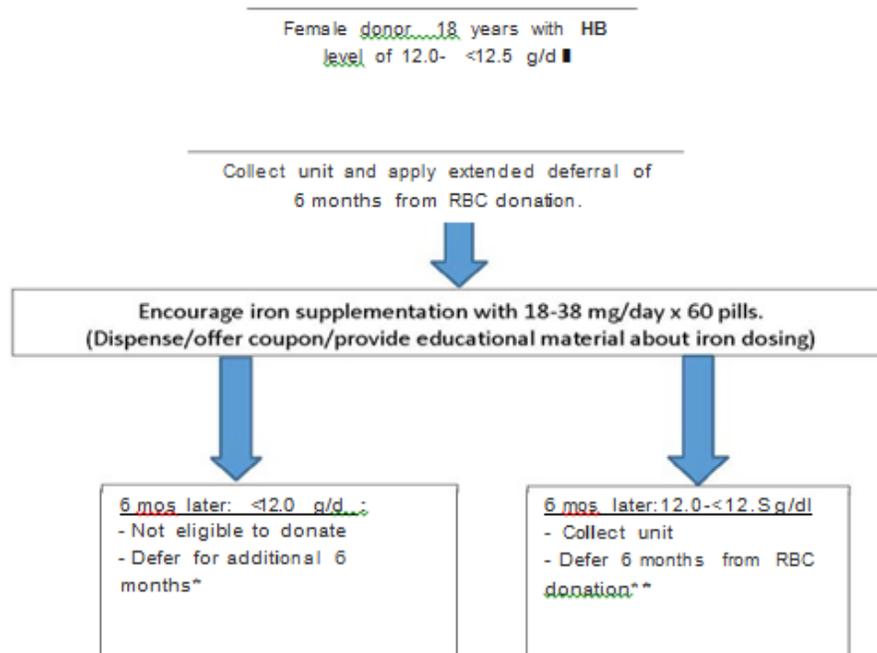
The AABB recommended flow sheets provide two different strategies that blood establishments could adopt into their procedures with or without modification. The approaches to managing the risk of iron deficiency rely on a combination of ferritin testing and extended deferrals, or extended deferrals alone for at risk donors. Both strategies include encouraging iron supplementation. The proposed flow sheets are shown below:

1. Management of risk for iron deficiency using ferritin testing



* Exceptions noted for ferritin 200 ng/mL or greater

2. Management of risk for iron deficiency using extended deferral



* 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.

Rationale supporting AABB proposed procedures

The AABB website provides a question and answer document explaining the rationale and scientific literature supporting the recommendations in the flow sheets. Below is a summary of some of the information listed.

1. Ferritin testing

It is well established that hemoglobin testing is not a good indicator of iron stores. Conversely, serum or plasma ferritin is a good indicator of tissue iron stores and has been studied alone or in combination with other tests to determine evidence of iron deficiency in blood donors. A low ferritin level correlates with decreased iron stores. However, elevated levels could occur in different clinical scenarios such as iron overload, inflammatory disorders, liver disease, or malignancy.

The serum ferritin level is typically less than 12-15 ng/mL in individuals with iron deficiency anemia. However, there are some studies that show that higher levels are more sensitive indicators of iron deficient erythropoiesis (17). Studies of ferritin in blood donors have used different cut-offs varying from 9-26 ng/mL to define iron deficiency. Some studies have used gender specific cut-offs. AABB selected the cut-off value of <26 ng/mL based on values used in recent U.S. studies of ferritin testing and iron supplementation in blood donors, including the Hemoglobin and Iron recovery Study (HEIRS) (18) and Strategies To Reduce Iron Deficiency Study (STRIDE) (19).

Ideally, ferritin determination should be performed and results obtained prior to blood donation. However, point-of-care or rapid testing for ferritin is not readily available. Ferritin testing is typically performed on an analyzer that may not be available at a blood collection facility. The AABB workgroup determined that prescreening a donor with hemoglobin levels between 12.0- 12.5 g/dL and asking them to return would be operationally difficult and decrease the likelihood of the donor returning for blood donation. The proposed AABB procedure assures a likelihood of more blood collections

and donor return. It is expected that a significant number of donors presenting with hemoglobin levels between 12.0- 12.5 g/dL will be repeat donors who are more likely to be iron deficient. However, they will undergo ferritin testing and will be advised on measures to mitigate iron deficiency.

Other countries have established programs to monitor ferritin levels of blood donors routinely. In Switzerland, ferritin levels of whole blood donors are measured at each donation. Results are typically available the next day and the blood bank physician informs and counsels donors whose ferritin levels are less than 10 ng/mL. In Denmark, ferritin testing is performed on the first donation and every ten subsequent donations. It may be performed more frequently based on previous results. Donors are provided with iron supplements based on ferritin and hemoglobin levels (20).

2. Deferral period

- a. For the procedure where a female donor has a hemoglobin level between 12 and 12.5 g/dL and ferritin testing is performed, AABB recommends that donors with ferritin levels less than 26 ng/mL should be deferred for 16 weeks. This recommendation is based on results of several studies:
 - The REDS II RISE study determined that the odds of iron deficiency is greater in donors returning for donation in less than 14 weeks (12).
 - The HEIRS study revealed that even though iron supplementation accelerates hemoglobin and iron recovery, ferritin levels recovered later (median 76 days) compared to hemoglobin levels (18).

The AABB workgroup determined that 16 weeks allows an adequate window for iron recovery.

- b. For the procedure where a female donor has a hemoglobin level between 12 and 12.5 g/dL and no ferritin testing, AABB recommends a 6 month deferral. The 6 month deferral is supported by the HEIRS study showing that 67% of participants who did not receive iron failed to recover their iron stores within 168 days (18).

3. Iron supplements (dosage and duration)

Iron supplementation in blood donors improves hemoglobin recovery, reduces deferrals due to low hemoglobin and minimizes the incidence of iron deficiency (14, 18, 19, 21, 22). Multiple studies exploring iron supplementation in blood donors have used varying doses of iron over different periods (23). The recommendations of 18 mg or 38 mg iron daily in the AABB flow sheet are based on results of the STRIDE study where donors took 19 or 38 mg of iron for 56 days. Both groups showed improvements in their iron status and venous hemoglobin. Even though the STRIDE study used 19 or 38 mg of iron, The AABB flow sheet recommends 18 mg or 38 mg because some multivitamins contain 18 mg of iron. Treatment duration in studies examining iron supplementation in blood donors have varied. AABB proposed iron supplementation over 60 days based on results of the HEIRS study that showed that when donors were administered 38mg of iron over 24 weeks, 88% of the of iron replacement occurred within the first 8 weeks (24).

4. Iron administration options

The AABB flow sheets provide different options for encouraging iron supplementation: dispensing iron, offering coupons, and providing educational material about iron supplementation. This is to allow operational flexibility within blood establishments.

There are studies that have examined the effectiveness of some iron administration

options. The STRIDE study evaluated whether material with information about a donor's iron status and recommended courses of action would encourage donors to take steps to mitigate iron lost from donation on their own (19). This study revealed equivalent ferritin recovery in the group that received iron status letters containing ferritin results compared to the iron supplementation group. In the group receiving iron status letters, iron supplements or delayed donation for 6 months was recommended if ferritin was low (< 26 ng/mL). Evaluation of donors' responses to the iron status letters at the end of the study found that most donors did take action to protect their iron status. A study of Swiss blood donors by O'Meara and coworkers revealed that ferritin testing and donor counseling by a physician providing results and options for encouraging iron recovery (including iron supplementation) decreased the incidence of predonation anemia and donation ineligibility (25). A study of Canadian donors informed of their low ferritin results revealed that notification reduced donor return rates and donation frequency. Qualitative interviews of the donors revealed that even though most donors took some kind of action (including iron supplementation) following notification of a low ferritin result, donors were not well informed about iron needs (26).

5. Compliance with iron supplementation

In order for iron supplementation to be effective, compliance with dosing and duration of treatment is necessary. Most studies of iron supplementation in blood donors generally noted a high compliance rate. One study reported poor compliance in about a quarter of female participants and a third of male participants. It should be noted that the definition of compliance varied (e.g. ingestion of all tablets versus ingestion of 90%) (23). Other than side effects, differences in compliance could be due to factors such as participation in a study, the variability in methods used to provide personalized iron education (e.g. donor counseled by blood center or personal physician), and availability of iron supplements.

Summary

The minimum normal hemoglobin level for U.S. females is 12.2 g/dL in Whites and 11.5 g/dL in Blacks (5). FDA finalized the donor eligibility rule to permit blood collections from female donors with hemoglobin levels between 12.0 to 12.5 g/dL provided additional steps or procedures acceptable to FDA are performed.

Female blood donors are commonly deferred for low hemoglobin and iron deficiency is frequently detected in these donors especially if they are premenopausal or repeat donors.

Based on the scientific data available, AABB has established flow sheets with proposed strategies that blood establishments could adopt into their procedures for collection of blood from female donors with hemoglobin levels between 12.0 and 12.5 g/dL. These options include ferritin testing and iron supplementation based on ferritin results, or extension of donation deferral periods and iron supplementation.

The FDA would like the Committee to discuss the risks and benefits of the proposed strategies for the collection of blood from females with hemoglobin levels between 12.0 – 12.5 g/dL or suggest alternate strategies. Considerations should include the scientific data available and operational feasibility.

Questions for the Committee

1. Please comment on the proposed procedures for collection of blood from female donors with hemoglobin values of 12.0-12.5 g/dL:
 - a. Collection of blood, ferritin testing, followed by iron supplementation and 16 week deferral if ferritin level is low.
 - i. Collection of blood prior to obtaining results of ferritin test result
 - ii. Proposed deferral period for females with low ferritin
 - iii. Iron supplementation options
 - b. Collection of blood, 6 month deferral, and iron supplements for 60 days. No ferritin testing.
 - i. Collection of blood without prior knowledge of ferritin levels
 - ii. Proposed deferral period
 - iii. Iron supplementation options
2. Please discuss any alternative procedures that FDA should consider to permit collection of blood from female donors with hemoglobin values of 12.0-12.5 g/dL

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