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Putting donor health first in strategies to mitigate donor iron deficiency

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Whole blood donation removes approximately 10% of the red blood cells (RBCs) from the donor. Since RBCs contain most of the iron in the body, removal of RBCs also removes a large amount of iron. The iron removed in a single whole blood donation is approximately equal to one-fourth the amount of storage iron in an average male and the entire amount of storage iron in an average female, which is needed to produce new RBCs after donation. Absorption of dietary iron sufficient to replace blood donation loss takes more than 180 days in donors who do not take daily oral iron supplements and approximately 90 days in those who do.¹ These recovery periods are much longer than the 56-day minimum whole blood interdonation interval in the United States. Consequently, frequent donation commonly depletes iron stores in both male and female donors leading to storage iron deficiency and then iron deficiency anemia. The high prevalence of iron deficiency in repeat blood donors was initially described in studies led by Finch and colleagues² and Simon and colleagues³ 40 years ago and characterized in more detail in the RISE^{4,5} and HEIRS¹ studies performed within the NHLBI-sponsored REDS program.

Iron deficiency is an important donor health concern with many associated adverse effects occurring even in the absence of anemia. These adverse effects on health include decreased cognitive function^{6,7} and fatigue,^{8,9} which may be associated with poor work or school performance; pica,^{10–12} which is the compulsive chewing of nonnutritional substances; and restless leg syndrome,^{11,12} which alters sleep habits. In addition, adequate iron stores in the mother are essential for proper neurologic development of the fetus,¹³ presenting an important health concern for premenopausal female donors who are considering pregnancy.

Another, perhaps underrecognized, adverse consequence of blood donation–induced iron deficiency is the unnecessary medical workups donors experience when unexpected iron deficiency anemia is identified during a routine physical examination. This scenario often occurs in men, who are allowed to continue donating blood even when they have iron deficiency anemia. These medical evaluations can take place because the previous 12.5 g/dL donation cutoff, as well as the current 13.0 g/dL donation cutoff, for hemoglobin (Hb) in the United States are below the lower limit of the reference range for Caucasian males, which is

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CONFLICT OF INTEREST

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13.7 g/dL for men less than 60 and 13.2 g/dL for men 60 and older.¹⁴ Only after negative results from extensive and costly medical testing for occult gastrointestinal bleeding is it verified that the iron deficiency was caused by frequent blood donation.

Teenage blood donors may be particularly vulnerable to adverse effects of iron deficiency from blood donation. Adequate iron is needed for myelination of nerve fibers during brain development, which continues in the teenage years.^{15,16} Perhaps most importantly, areas in the temporal lobe undergo extensive maturation during the teen years and early 20s.¹⁶ Failure of these areas to properly develop can be associated with severe mental illnesses, including adult-onset schizophrenia.¹⁷ Even iron-replete donors may experience transient periods of postdonation iron deficiency lasting approximately 3 months after a single whole blood donation,¹ a period that is likely longer after a double-RBC donation. Since some teenagers donate four or even five times in a single school year, even those that remain iron replete may be experiencing multiple periods of transient iron deficiency. The potential adverse effects of donation-induced iron deficiency on brain development in teenagers should be considered as policies for collection of blood from teenagers are revised to more restrictive practices using the principle of “first do no harm.”

Iron deficiency in blood donors occurs because there is no screening test performed to identify it and defer iron-deficient donors. Measures of Hb or hematocrit do not accurately reflect donor iron stores, which are best assessed by measurement of plasma or serum ferritin. A serum ferritin value of not more than 12 ng/mL is a highly specific marker for the absence of iron stores in the marrow, as determined by comparison with results from Prussian blue staining of a marrow aspirate.¹⁸ Thus, donors with a ferritin level of not more than 12 ng/mL have severe iron deficiency with no iron in the marrow available for synthesis of new RBCs. During our studies of frequent donors,^{1,4,19} we have routinely observed subjects who passed the Hb screen and donated 1 unit of blood, only later to find that their predonation ferritin level was not more than 12 ng/mL, confirming that Hb is a poor marker for iron deficiency in blood donors. While ferritin level of not more than 12 ng/mL is a highly specific marker for iron deficiency, it is not a particularly sensitive marker for iron deficiency. This shortcoming means that there are many individuals with ferritin levels of more than 12 ng/mL, who have absent marrow iron stores. In an otherwise healthy population, such as blood donors, the ferritin cutoff can be raised to increase the sensitivity for detecting iron deficiency without losing specificity.²⁰ It appears that a reasonable cutoff that optimizes the sensitivity and specificity for plasma ferritin is not more than 26 ng/mL.⁴ This level correlates with a cutoff of not more than 30 ng/mL for serum ferritin, which is approximately 10% higher than plasma measurements.²⁰

In this issue of **TRANSFUSION**, Goldman and coworkers²¹ present findings from their operational implementation of ferritin testing to mitigate iron deficiency in 12,595 blood donors across Canada. Plasma ferritin testing was performed on a retention tube collected before donation. A letter was sent to those with a ferritin level of less than 25 ng/mL approximately 2 weeks after donation. The letter told the donor they had low ferritin levels, which means they did not have enough iron to meet their needs. The letter then recommended halting subsequent donation until the cause of the low ferritin was identified by their family physician and their iron stores had returned to normal. Donors with ferritin

levels of more than 25 ng/mL were not sent a letter. At approximately 1 year of follow-up, among donors returning to donate, those receiving a low ferritin letter increased ferritin by approximately 15 ng/mL, while those not receiving a letter decreased ferritin by approximately 17 ng/mL. The wide profile of ferritin testing across Canadian blood donors identified iron deficiency in 32% of first-time female donors and 3% of first-time male donors. This frequency increased to 65% in repeat female donors and 42% in repeat male donors, both of whom donated approximately two times per year. This high prevalence of iron deficiency is similar to that found in donors in the United States. As a result of this study, the minimum interdonation interval for females in Canada will be increased to 84 days and the minimum Hb cutoff increased to 13.0 g/dL for males.

The findings of Goldman and coworkers are consistent with those of donors randomized into the iron status information group of the STRIDE study.²² The STRIDE subjects were sent a letter informing them of their ferritin and recommended actions. At the end of the 2-year study, they had iron status identical to donors randomized to directly receive iron pills. An important difference between STRIDE and the study by Goldman and colleagues is that iron status information donors in STRIDE with ferritin levels of not more than 26 ng/mL were instructed either to begin to take iron supplements or to delay donation for at least 6 months, rather than to see their physician. All subjects enrolled in STRIDE were frequent donors and blood donation was by far the most likely cause of their iron deficiency. The findings from these two studies, as well as the earlier finding of O'Meara and coworkers,²³ provide ample evidence that donors given accurate information about their iron status in the form of ferritin test results will take recommended actions to mitigate iron deficiency on their own. Another benefit of ferritin testing is that donors with undiagnosed hemochromatosis can be identified and advised not to take iron after donation.

So, where are we in regard to the possibility for widespread ferritin testing in blood donors? Goldman and coworkers have demonstrated that testing and providing follow-up letters to donors is operationally feasible at a cost of about \$4 US. The feasibility of ferritin testing is further supported by the success of cholesterol testing programs in place at blood centers in the United States, as well as the testing of Hb A1C to diagnose diabetes and prediabetes in high school donors at one US center. These demonstrate additional laboratory testing is affordable and donors can be provided with individualized results. It is important in the design of programs to mitigate iron deficiency to focus first on what is best for the health of the donor and then to build operationally efficient programs around this philosophy. For example, programs should not be focused only on O- donors. Since iron deficiency occurs before iron deficiency anemia, programs should not focus only on donors experiencing a low Hb deferral due to iron deficiency anemia but all donors at risk for iron deficiency as identified by ferritin testing. Both male and female donors become iron deficient with frequent donation,⁵ so programs should include male, as well as female, donors. Based on the high prevalence of iron deficiency in the study by Goldman and coworkers, it appears that all females and all males donating more than once per year would benefit from ferritin testing.

Findings from STRIDE have demonstrated that 19 mg of iron daily for 60 days after donation is as effective as 38 mg iron for mitigation of iron deficiency in frequent donors.²¹

This iron dose is approximately the amount of iron present in over-the-counter multiple vitamins with iron. It was well tolerated and not associated with increased adverse events compared to those randomized to receive placebo. Thus, advising donors with low ferritin to take a multiple vitamin with iron for 60 days between donations seems reasonable. It is important to note that iron absorption is highest immediately following donation.^{1,24} Donors should be advised to begin taking iron as soon as possible after donation, rather than in the few days preceding their next anticipated donation so they can “pass the iron test.” Magnussen and her team in Denmark run a program that monitors donor iron and Hb status and provides targeted iron therapy based on the laboratory test results.^{25,26} This program has successfully mitigated donor iron deficiency and reduced low Hb deferrals setting a standard for other centers to emulate.

Over the long term, development and implementation of programs to mitigate donor iron deficiency will benefit the donor and the blood center and perhaps raise awareness of iron deficiency in the general population, thereby having a positive impact on overall public health. In the meantime, we should begin to adopt programs to mitigate iron deficiency in our donors with particular emphasis for teenage donors, females in their childbearing years, and frequent donors, where the potential for harm may be greatest. Programs that include reducing donation frequency, iron supplementation through direct provision or medical advice, and ferritin testing with recommendations for donor action based on iron status appear to be the best options, as we deal with these growing concerns.

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