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## Iron deficiency in whole blood donors

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Each year, 5 million regular donors meet almost half the transfusion needs of the United States by voluntarily giving their blood. In this issue of **Transfusion**, we learn how well the needs of these committed donors are being met from an analysis of enrollment data from the Retrovirus Epidemiology Donor Study-II (REDS-II) Donor Iron Status Evaluation (RISE) study of the National Heart, Lung, and Blood Institute.<sup>1</sup> The RISE study is the largest and most comprehensive study yet conducted of iron deficiency in blood donors, with an enrollment of 2,425 women and men. The results are alarming. Among frequent donors, two-thirds (66%) of the women and almost half (49%) of the men were iron deficient.<sup>1</sup> The true prevalence of iron deficiency among regular donors is surely higher; the RISE study enrolled only frequent donors who had been *accepted* for donation, excluding those deferred for a low hemoglobin concentration. Moreover, the enrolled, iron-deficient donors then each donated a unit of whole blood, further depleting their body iron by an additional 200 to 250 mg. Neither these loyal donors nor the national blood supply are well served by the collection practices and regulatory framework that have produced widespread iron deficiency among those who regularly give their blood.

The RISE study used the best laboratory measures available, the plasma ferritin and soluble transferrin receptor concentrations,<sup>2</sup> to detect “iron-deficient erythropoiesis,” the stage of iron depletion in which new red blood cell production is restricted by a lack of iron. The rate of erythropoiesis is coordinated with iron availability by iron regulation of erythroid differentiation. Iron deficiency reduces the responsiveness of erythroid progenitors to erythropoietin, apparently through an iron-aconitase-isocitrate pathway.<sup>3</sup> With a dearth of iron, decreased erythroid utilization for red blood cell production helps preserve the supply of iron for vital functions in other tissues. This protection is incomplete. Iron deficiency, even in the absence of anemia, is associated with decreased physical endurance and work capacity, fatigue, and impairments in attention, concentration, and other cognitive functions.<sup>4–7</sup>

A principal objective of the RISE study is to evaluate the effects of blood donation on hemoglobin concentration and body iron in donors in the United States.<sup>1</sup> The enrollment data are cross-sectional, so the effects of donation on iron deficiency among first-time and “reactivated” donors (i.e., those with no donations in the previous two years) will only become apparent in subsequent analyses of their fate during the two years of follow up in the study. Nonetheless, for frequent donors (enrolled as women who had given more than two, and men who had given more than three, donations in the past year) some immediate conclusions can be drawn from the present RISE results.

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First, at enrollment, an increase in the number of red blood cell donations in the preceding two years was associated with only a modest decrease in venous hemoglobin concentration.<sup>1</sup> This observation should not provide false comfort. As Cable and colleagues note, donors made anemic by iron depletion would have been deferred from previous donation and not enrolled in the group of frequent donors.<sup>1</sup> Given the high (10%) overall rate of deferral from donation for a low hemoglobin concentration at the six centers participating in the RISE study,<sup>8</sup> this loss of donors is likely substantial. Subsequent analyses of the attrition of the frequent donors enrolled in the RISE study should provide a quantitative estimate of the actual magnitude of the decline in hemoglobin concentration with repeated donation.

Second, at enrollment, an increase in the number of red blood cell donations in the preceding two years was the strongest predictor of iron deficiency among frequent donors. Women who had donated 2 to 4, and men who had donated 3 to 4 units in the preceding two years had a 14-fold increase in the risk of iron deficiency compared to first-time donors; those who had donated 10 or more units had a more than 50-fold increase.<sup>1</sup> Like each of the large cross-sectional studies of blood donors conducted over the past three decades,<sup>9–11</sup> the RISE study documents that more frequent donation, with attendant greater iron losses, is the predominant factor leading to iron deficiency. The unavoidable conclusion is that present blood collection practice fails to protect committed blood donors from iron deficiency.

Third, women of childbearing age bear the brunt of donation-induced iron deficiency.<sup>1</sup> In the United States, the requirements for whole blood donation, a minimum acceptable hemoglobin concentration of 12.5 g/dL and a minimum interval between donations of eight weeks,<sup>12, 13</sup> are identical for women and men. The requirements of iron physiology are not. Compared to men, menstruating women have higher daily iron requirements (1.5 vs. 1.0 mg) owing to menstrual losses of iron in hemoglobin and the large iron requirements of pregnancy, lower storage iron reserves (300 vs. 1000 mg) and a greater prevalence of iron deficiency.<sup>14</sup> At the six centers participating in the RISE study, 1.6% of attempts at donation by men but 17.7% of attempts by women end in deferral for a low hemoglobin concentration.<sup>8</sup>

Fourth and last, neither self-selected and -administered iron supplements nor the usually recommended iron-rich components of the diet had appreciable effects on the risk of iron-deficient erythropoiesis. This observation suggests that recommendations typically given at blood centers to donors deferred because of a low hemoglobin<sup>15</sup> are ineffectual in preventing iron deficiency.

The high prevalence of iron deficiency among those who regularly give blood, documented in the RISE study,<sup>1</sup> is of special importance for both the safety of donors and the preservation of the national blood supply. Iron deficiency accounts for up to 70% of deferrals for a low hemoglobin concentration,<sup>9</sup> a critical cause of donor loss. After deferral for low hemoglobin, 15% of repeat donors never return and another 14% return only once.<sup>16</sup> Over a more than 4-year period of follow up, deferral for a low hemoglobin concentration decreased the donation rate among repeat donors by more than 30%.<sup>16</sup> With replete iron stores, erythropoiesis can readily be increased to replace red blood cells removed at donation in six to eight weeks.<sup>17</sup> By contrast, after deferral with iron deficiency, the future capacity of donors to give blood is restricted for prolonged periods. With iron-deficient erythropoiesis and without iron supplementation, the time to replace donated red blood cells depends upon the rate of dietary iron absorption. Maximum iron absorption from a usual Western diet is at most 3 to 4 mg per day. Consequently, after deferral with iron deficiency, restoring the hemoglobin concentration to pre-donation concentrations may require an average of 12 to 18 weeks in men, and 14 to 24 weeks, or more, in women of childbearing age. Rebuilding iron stores to pre-donation levels needs additional periods of like, or longer, duration.

Cable and colleagues<sup>1</sup> note that cardioprotective health benefits of iron depletion have been proposed for blood donors.<sup>18</sup> The iron-heart hypothesis is that “the greater incidence of heart diseases in men and postmenopausal women compared with the incidence in premenopausal women is due to higher levels of stored iron in these two groups.”<sup>19</sup> Initial small studies comparing blood donors with non-donors found reduced rates of heart disease among male donors<sup>20,21</sup> and only among male donors who did not smoke.<sup>22</sup> A subsequent, much larger comparison of donors with non-donors found no reduction in the risk of myocardial infarction with blood donation.<sup>23</sup> Studies comparing frequent with infrequent donors found a reduced risk of cardiovascular events<sup>24</sup> and greater flow-mediated dilation in the brachial artery<sup>25</sup> among men and postmenopausal women. By contrast, the sole prospective, randomized clinical trial of phlebotomy to reduce body iron stores, the Iron (Fe) and Atherosclerosis Study (FeAST), found no significant effect on all-cause mortality or on death plus nonfatal myocardial infarction and stroke.<sup>26</sup> Overall, the majority of epidemiologic studies have found no significant association between the risk of cardiovascular disease and body iron stores.<sup>27–37</sup> In particular, iron stores were not associated with the risk of coronary heart disease in women, whether pre- or postmenopausal.<sup>38</sup> On balance, a decreased risk of heart disease with iron depletion is unproven,<sup>39–41</sup> even if not disproven,<sup>42–46</sup> by the evidence gathered over the past thirty years. For those regular donors with the highest prevalence of iron deficiency, women of childbearing age, no evidence of cardioprotection has been reported. Voluntary donors give their blood altruistically, without anticipation of personal benefit but with the expectation of no harm from donation. An unproven, hypothetical health benefit does not compensate for the ill effects of iron deficiency on donors and donations.

Almost a decade ago, at a workshop on maintaining iron balance in women blood donors of childbearing age that was co-sponsored by the National Heart, Lung and Blood Institute, the American Association of Blood Banks, America’s Blood Centers, and the American Red Cross, the view was advanced that recruitment of new donors was more “cost-effective” than retention of donors by measures to prevent iron deficiency.<sup>47</sup> At the workshop, no final determination was made about the relative value of the two approaches. Still, recruitment of new donors to replace donors who are lost because of iron deficiency seems to have remained the *de facto* practice at most blood centers. Cable and colleagues conclude that the findings of the RISE study raise concerns about the “ability of the current donor standards to prevent and detect significant adverse donor sequelae related to iron depletion” and should lead to consideration of interventions to better manage donor iron balance.<sup>1</sup> Reexamination of measures to prevent iron deficiency in women of childbearing age by iron replacement after donation<sup>7,47–51</sup> may now be in order. The U.S. Food and Drug Administration is currently considering changes in the hemoglobin and hematocrit standard and in the interval between donations to better protect donors.<sup>52</sup> These initial RISE results may help lead to correction of our deficiencies in the management of iron balance in whole blood donors, with benefits both for those who give their blood and for the national blood supply.

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