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EDITORIAL

The detrimental impact of ferritin "normal" ranges on diagnosis of bleeding disorders in women

In this editorial, we use the term "women" to highlight the experiences of and care gaps for women with nonanemic iron deficiency (NAID) and iron deficiency anemia (IDA) and the term "females" in reference to the biological capacity to menstruate, become pregnant, give birth and lactate. We acknowledge that these terms are exclusive, and recognize that these experiences may also apply to all people with the anatomy that allows for menstruation, pregnancy, and childbirth, including girls, transgender men, intersex people, and gender nonbinary individuals [1–3].

Iron deficiency is the most widespread micronutrient deficiency in the world and is the leading cause of years of living with disability among women [2,4,5]. Nonanemic iron deficiency (NAID) progresses to iron deficiency anemia (IDA) when there are insufficient iron stores to sustain red blood cell production [2]. Iron deficiency, with or without anemia, is associated with many negative consequences, including fatigue, cognitive impairment, impaired physical function, and lower health-related quality of life [6]. NAID and IDA impact many females of reproductive age largely due to iron losses from vaginal blood loss [2,7]. NAID and IDA are extremely prevalent among women. In fact, data from the US National Health and Nutrition Examination Survey and Canadian outpatient community laboratories estimated the prevalence of NAID at approximately 40% of all non-pregnant females and IDA at approximately 13% [4,8]. It is a common misconception that the complete blood count alone is sufficient for the diagnosis and screening of iron deficiency. Anemia and microcytosis typically manifest only after sustained iron deficiency and/or significant blood loss [9]. Furthermore, an abnormal mean corpuscular volume was observed in only 44% of women with confirmed IDA, indicating that mean corpuscular volume is not a reliable marker for identifying iron deficiency [8].

Serum ferritin is the most reliable diagnostic test for iron deficiency [10,11]. A ferritin clinical decision limit of <30 μg/L is generally the accepted threshold for the diagnosis of iron deficiency in adults [10–13]. However, many clinical laboratories rely on a far lower limit of normal (LLN) to flag abnormally low ferritin for healthcare providers [14]. In fact, a 2021 survey reported that 78.2% (18/23) of North American clinical laboratories used a serum ferritin LLN <15 μg/mL [14]. The LLN is derived from data from samples of apparently healthy individuals, and statistical techniques are then performed to determine the reference interval using the 2.5th and 97.5th percentiles [15]. A recent systematic review of 62 studies determined that reported ferritin LLNs are at high risk of bias given the lack of exclusion of individuals at risk of iron deficiency (eg, based on bleeding history) and lack of adherence to Clinical and Laboratory Standards Institute recommendations in the presumed "normal" reference sample [15]. Importantly, the systematic review found that many serum ferritin assays have an LLN well below 30 μg/L (median, 8 μg/L in females and 25 μg/L in males) [15].

The discrepancy between a clinically relevant, evidence-based decision limit and the lower limit of "normal" for serum ferritin levels contributes to underdiagnosis and undertreatment of iron deficiency. Management of NAID/IDA involves repletion of iron stores via oral or intravenous routes and identifying and managing the underlying cause of iron deficiency [7]. It is likely that misclassification of ferritin-iron deficiency thresholds decreases the opportunity to consider the diagnosis of inherited bleeding disorders, especially among women. An inappropriate lower limit of "normal" likely precludes healthcare providers from investigating the cause of iron deficiency as it has not been structurally flagged as abnormally low by the laboratory. Given the high patient volumes, abnormal laboratory flags play a significant role in influencing clinician behavior and serve as a prompt for further investigation [16].

In non-pregnant women, the most common cause of iron deficiency is heavy menstrual bleeding (HMB), defined as a loss of >80 mL of menstrual blood per cycle based on early population-based studies [6,17,18]. This definition of HMB was based on the upper limit of normal menstrual blood loss due to a greater prevalence of iron deficiency with vaginal blood losses above 60 mL [2,6,17,18]. Unfortunately, in clinical practice, this definition remains poorly operationalized, as quantifying vaginal blood loss is a challenge for patients and clinicians alike [2,19].

It is estimated that HMB affects nearly 90% of women with an underlying bleeding disorder [20]. Further complicating matters, the discussion of HMB is stigmatized, which promotes symptom normalization and the inability of individuals to differentiate between normal and heavy periods—especially if family members are also affected [1,21]. The challenges with diagnosing HMB and the lack of screening recommendations for iron deficiency in women of reproductive age likely synergistically contribute to diagnostic delays for inherited bleeding disorders. As an example, the diagnostic delay for von Willebrand disease, the most common bleeding disorder, is 6 years

longer for females compared with males (11.6 ± 16.4 years vs 7.7 ± 16.6 years, P = .002), despite a similar age at first bleed and more frequent healthcare encounters for bleeding episodes [1,21–24].

Given the propensity of bleeding among women with bleeding disorders, NAID and IDA are very common in this population yet likely grossly underreported due to undertesting or erroneous definitions of iron deficiency. Current prevalence estimates for iron deficiency in this population range from 22% to 61% based on single-center retrospective studies [25,26].

We hypothesize that the widespread adoption of evidence-based ferritin clinical decision limits will contribute to reduced diagnostic delays of inherited bleeding disorders among women. In Ontario, the most populous province in Canada, a multidisciplinary grassroots initiative called "Raise the Bar" changed the LLN of serum ferritin to a clinical decision limit of <30 μg/L for adults and <20 μg/L for children across the largest Canadian community laboratories. Coupled with the change, a comment flagging the diagnosis of iron deficiency connects clinicians to additional information (https://www.hemequity.com/raise-the-bar-home). Future work will evaluate changes in the prevalence of NAID and IDA and their impact on healthcare utilization over time pre- and postimplementation.

The widespread reliance on outdated and inaccurate lower limits of serum ferritin, compounded by the inconsistent guidelines, continues to hinder the proper diagnosis and treatment of NAID and IDA. This systemic issue not only perpetuates iron deficiency but likely also delays the diagnosis of inherited bleeding disorders, particularly among women. Structural change and evidence generation are needed to improve patient outcomes and access to care to reduce health disparities.

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M.S. and G.H.T. conceptualized the article. G.H.T. drafted the article. M.S. and G.H.T. critically reviewed the article for content and approve the final version.

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