ORIGINAL ARTICLE

Optimizing hemoglobin thresholds for detection of iron deficiency among reproductive-age women in the United States

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Iron deficiency (ID) affects 9%–16% of US women with well-documented morbidity in academic performance, mood, and concentration. Current ID screening depends on the detection of low hemoglobin (ie, anemia, <12.0 g/dL). However, anemia is a late-stage indicator of ID. The study hypothesis was that using higher hemoglobin thresholds would optimize ID screening. The objective was to assess the sensitivity and specificity of hemoglobin to detect ID among nonpregnant, reproductive-age women of 12–49 years and to determine if psychometric characteristics varied by age and race. This cross-sectional study used National Health and Nutrition Examination Survey 2003–2010 data. ID was defined as body iron, calculated using ferritin and transferrin receptors. Logistic regression and receiver operating characteristic (ROC) curves were used to model the predictive probability of ID by hemoglobin values. ID prevalence by body iron was 11.5% (762/6602). Using <12.0 g/dL, hemoglobin had a sensitivity of 42.9% (95% confidence interval (CI) = 39.4%, 46.4%) and specificity of 95.5% (95% CI = 95.0%, 96.0%) for ID. The ROC curve was optimized at the hemoglobin threshold of <12.8 g/dL with the sensitivity and specificity of 71.3% (95% CI = 68.0%, 74.5%) and 79.3% (95% CI = 78.2%, 80.3%), respectively. The probability of ID at this threshold was 13.5% (95% CI = 11.3%, 15.9%). Hemoglobin better predicted ID among older (22–49 years) vs younger (12–21 years) women (c-index 0.87 vs 0.77, $P < 0.001$). Among nonpregnant, reproductive-age women, current hemoglobin thresholds are insufficient to exclude ID. A threshold of <12.8 g/dL improves the detection of ID. (Translational Research 2016;■:1–9)

Abbreviations: AUC = area under the curve; ID = iron deficiency; NHANES = National Health and Nutrition Examination Survey; ROC = receiver operating characteristic; US = United States

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INTRODUCTION

Iron deficiency (ID) is the most common form of nutritional deficiency in the United States.[1,2] Although ID affects all age groups, reproductive-age women are at higher risk secondary to increased iron demands from menstrual blood loss and pregnancy. It is estimated that 9%–16% of reproductive-age US women are iron deficient, whereas 2%–5% are anemic.[1,3,4]

Anemia is a late-stage indicator of ID. To develop anemia, iron-deficient individuals must have significantly depleted the body's iron stores.[1] However, even

AT A GLANCE COMMENTARY

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Background

Current iron deficiency (ID) screening depends on the detection of low hemoglobin (ie, anemia <12.0 g/dL). However, as anemia is a late-stage indicator of ID, this strategy fails to identify most iron-deficient, reproductive-age women.

Translational Significance

Using National Health and Nutrition Examination Survey 2003–2010 data, logistic regression and receiver operating characteristic curves modeled the predictive probability of ID by hemoglobin. Using a hemoglobin threshold of <12.8 g/dL optimized the sensitivity and specificity for ID. When screening reproductive-age women for ID, a higher hemoglobin threshold may better inform clinical decision-making regarding further iron studies.

nonanemic iron-deficient women have been shown to experience significant morbidity including poor academic performance, mood lability, and concentration difficulty, which is improved with iron supplementation.[5-10]

Recognizing the importance of detecting ID, the Centers for Disease Control and Prevention recommends testing all nonpregnant women for ID anemia "every 5–10 years throughout their childbearing years during routine health examinations."[1,2] Because of the lack of a single, simple, and inexpensive test for ID, screening is based on the detection of anemia with hemoglobin levels, which continues as a routine practice despite low sensitivity and specificity for detection of ID.[1,2,11,12] Hemoglobin is a protein within red blood cells responsible for the delivery of oxygen to body tissues.[13] The hemoglobin protein itself contains iron, and the hemoglobin level is thus a reflection of the amount of functional iron in the body. Changes in hemoglobin levels only occur in the late stages of ID, making a decline in hemoglobin to anemic ranges, a late indicator of ID.[1]

Although ID is perhaps the most common etiology of anemia among US women, anemia has many causes, and hemoglobin norms for detecting anemia were not designed solely to optimize the detection of ID.[10] In clinical practice, higher hemoglobin concentrations, aside from polycythemia, are often equated with better iron status. Yet, the diagnostic accuracy of using hemoglobin as a screening tool for ID is rarely discussed despite its routine use.

The objective of this study was to determine the optimal hemoglobin threshold that maximizes the sensitivity and specificity for detecting ID among nonpregnant, reproductive-age women of 12–49 years using National Health and Nutrition Examination Survey (NHANES) 2003–2010 data. As normal hemoglobin values vary by age, adolescent and young adult (12–21 years) and older (22–49 years) reproductive-age women were analyzed separately.[1,2] It is anticipated that this information may enhance the value of hemoglobin testing for ID in clinical care and guide the decision to pursue additional iron studies.

MATERIALS AND METHODS

Study participants. The NHANES is a cross-sectional program of periodic surveys to assess the health and nutritional status of the US population.[14] The nationally representative surveys combine household interviews and physical examinations conducted in mobile examination centers by the National Center for Health Statistics, Centers for Disease Control and Prevention. The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. Participants are selected via a stratified multistage probability with oversamplings of certain groups (eg, African Americans and Hispanics) to produce reliable statistics.[14] This project was given a "not human research" determination by the Penn State College of Medicine Institutional Review Board.

This study included all women aged 12–49 years with hemoglobin, ferritin, and soluble transferrin receptor laboratory values recorded in NHANES 2003–2010. Because of variations in hemoglobin by age, younger (12–21 years) and older (22–49 years) women were examined separately.[1,2] As hemoglobin values also vary by race, Black and non-Black women were examined separately.[15] Participants were excluded for a history of blood transfusion, as this suggests their ID may have causes (eg, trauma and malignancy) other than the ID most commonly managed in preventive care.[10] Pregnant or breastfeeding participants were also excluded. Finally, those with cancer, malignancy, and chronic kidney or liver disease were excluded, but these questions were only asked for participants older than 20 years. As acute and chronic infection or inflammation may influence the iron indices, consistent with Cogswell et al,[4] we also excluded participants with a white blood cell count $>10.0 \times 10^3/\mu$L or a C-reactive protein >0.6 mg/dL.

Laboratory parameters. Hemoglobin concentration is a surrogate for the amount of functional iron in the