EARLY DIAGNOSIS AND MODERN TREATMENT STRATEGIES IN IRON DEFICIENCY ANEMIA CLINICAL SIGNIFICANCE OF FERRITIN AND TRANSFERRIN SATURATION

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Abstract: Iron deficiency anemia is the final hematological expression of a process that may begin with depletion of iron stores long before hemoglobin falls. Its recognition therefore requires more than identifying microcytosis. Ferritin describes stored iron, whereas transferrin saturation reflects the iron available for erythropoiesis; their diagnostic value depends on inflammation, renal function, recent treatment, and the probability of ongoing blood loss. This narrative review examines how these markers guide early diagnosis, investigation of the underlying cause, selection of oral or intravenous replacement, and assessment of response. Particular attention is given to apparently contradictory results, such as low transferrin saturation with preserved ferritin, and to the distinction between improved absorption with alternate-day dosing and proven clinical superiority. Durable treatment requires correction of both the iron deficit and its source. A structured follow-up plan is essential because normalization of hemoglobin alone does not establish that stores are replenished or that recurrent bleeding has been excluded.

Keywords: iron deficiency, ferritin, transferrin saturation, iron replacement, inflammation

Methods

This focused narrative review synthesizes clinical guidance and relevant primary study reports identified through targeted searches of guideline publishers, PubMed, and regulatory sources. Sources were selected for their relevance to diagnostic interpretation,

treatment selection, and longitudinal care. Findings are discussed qualitatively; no systematic-review claim or pooled effect estimate is made.

Introduction

Iron deficiency anemia frequently presents through symptoms shared with many other disorders, including fatigue, reduced exercise tolerance, palpitations, and difficulty concentrating. This creates two opportunities for diagnostic error: attributing nonspecific symptoms to iron deficiency without confirming it, and dismissing deficiency because hemoglobin or mean corpuscular volume remains normal. The clinical task is to establish whether iron supply is inadequate, determine why, and decide how quickly replacement is required.

Blood loss, impaired absorption, and increased requirements may coexist. Heavy menstrual bleeding does not exclude gastrointestinal disease, and chronic inflammation does not exclude depleted stores. The aim of this review is to connect laboratory interpretation with a practical treatment pathway rather than to treat ferritin as an isolated target.

Interpreting Thresholds and Conflicting Results

The initial workup should establish the blood count pattern, reticulocyte response, iron status, and relevant inflammatory context. A normal mean corpuscular volume does not exclude early deficiency, while microcytosis also occurs in thalassemia and other disorders. History should address menstrual and gastrointestinal bleeding, donation, diet, pregnancy, bariatric surgery, and medicines that promote bleeding. Celiac testing and gastrointestinal investigation are selected according to the clinical setting. Unexplained iron deficiency anemia in an adult at risk of gastrointestinal malignancy warrants investigation even when replacement produces a prompt improvement.

In otherwise healthy adults, ferritin below 15 micrograms/L strongly indicates absent stores, while values below 30 micrograms/L commonly support iron depletion. These thresholds are less reliable when inflammation increases ferritin independently of stored iron. WHO guidance allows a higher threshold in adults with inflammation, but this should not be confused with disease-specific treatment criteria in chronic kidney disease or heart failure. A transferrin saturation below approximately 20% suggests restricted circulating iron availability; it does not identify the mechanism on its own [1, 2].

Serum iron varies with timing, recent intake, and illness, so a single low result is insufficient. A preserved ferritin with low transferrin saturation should prompt consideration of inflammatory restriction, combined absolute deficiency, liver disease, or recent iron administration. C-reactive protein, renal function, reticulocyte hemoglobin, and the clinical history help resolve uncertainty. Soluble transferrin receptor can be useful where available, although assay differences complicate universal cutoffs. The purpose of

additional testing is to change a clinical decision, especially whether to investigate occult loss or replace iron, rather than to generate an increasingly large panel.

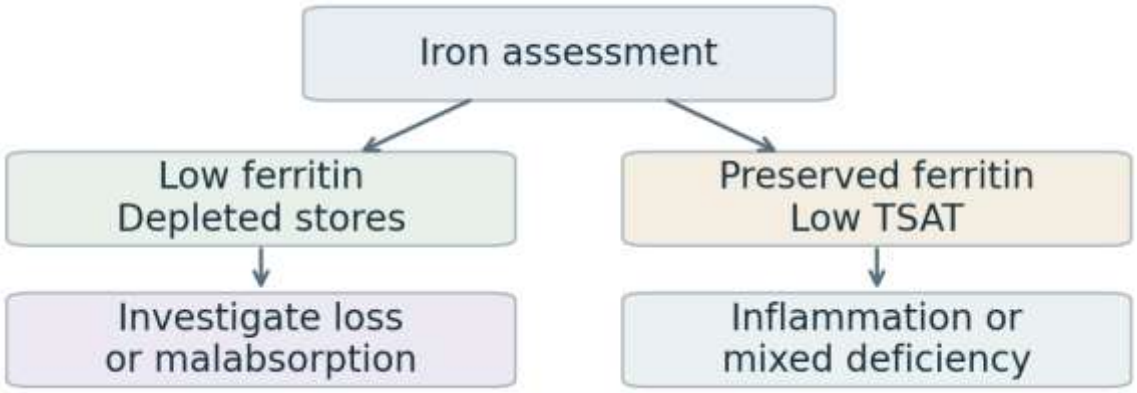


Figure 1. Ferritin and Transferrin Saturation

Evidence Behind Oral and Intravenous Replacement

Oral iron induces a temporary rise in hepcidin that can reduce absorption from a subsequent dose. Stable-isotope studies by Stoffel and colleagues demonstrated higher fractional absorption with alternate-day administration than with consecutive-day dosing in iron-depleted women. This provides a physiological explanation for avoiding unnecessarily frequent doses, but absorption studies do not establish that one schedule restores hemoglobin faster in every patient [4].

The AGA practice update supports oral treatment at most once daily and recognizes alternate-day dosing as a tolerable option. Route selection should reflect the cause of deficiency, the urgency of correction, previous response, and patient preference. Intravenous treatment is useful when oral iron is not tolerated, absorption is impaired, or iron stores fail to improve despite an adequate trial [3]. It also requires formulation-specific precautions. Infusion reactions require trained staff and observation, while repeated courses of some preparations can cause clinically important hypophosphatemia. The appropriate response to intolerance is a deliberate change in formulation, schedule, or route, not repeated prescriptions that the patient cannot take. Transfusion is reserved for the clinical consequences of severe anemia and does not replenish the underlying iron deficit.

Table 1. Iron Marker Patterns

Pattern	Likely interpretation	Next consideration
Low ferritin, low TSAT	Absolute iron deficiency	Identify losses or malabsorption
Normal/high ferritin, low TSAT	Inflammatory restriction or mixed anemia	Assess inflammation and comorbidity
Microcytosis with preserved iron indices	Alternative or combined cause	Consider hemoglobinopathy
Poor response to oral iron	Adherence, absorption, loss, or wrong mechanism	Reassess before escalation
Recent IV iron	Ferritin may be transiently high	Interpret after a suitable interval

Response Assessment and Prevention of Recurrence

A follow-up blood count within the early weeks of treatment establishes whether erythropoiesis is recovering. A rising hemoglobin supports the working diagnosis, but an inadequate response requires a structured review of adherence, gastrointestinal adverse effects, continued bleeding, malabsorption, inflammation, and competing deficiencies. The clinician should also reconsider whether the original anemia was caused by iron deficiency at all.

Replacement commonly continues after hemoglobin normalizes so that stores can recover. Ferritin should be interpreted at an appropriate interval after intravenous treatment because an early increase may reflect administered iron rather than stable long-term repletion. Subsequent monitoring should be more frequent when losses continue or the cause remains unresolved [1, 3].

In settings with limited specialist access, a useful minimum pathway combines a blood count, ferritin, transferrin saturation when available, and documented reassessment. Referral priority should depend on unexplained or recurrent deficiency, gastrointestinal alarm symptoms, severe anemia, and failure of replacement. A low-cost iron prescription has limited value if it repeatedly postpones investigation of the source. Clear communication between primary care, gynecology, and gastroenterology helps prevent this cycle.

For example, low transferrin saturation with a ferritin in the reference range during active inflammatory disease should not be labeled iron replete without further assessment. A history of recurrent gastrointestinal bleeding may make a mixed mechanism more likely.

The actionable question is whether replacing iron will address a demonstrated deficit and whether the source requires urgent investigation. Repeating iron indices after an acute illness can help when the clinical situation permits, but it should not defer investigation of concerning symptoms. Recording the reason for selecting oral or intravenous therapy makes later treatment failure easier to interpret.

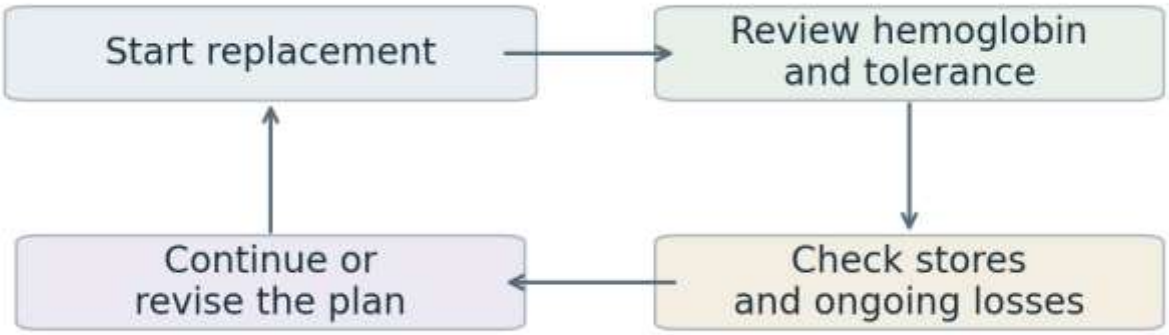


Figure 2. Iron Replacement Review

Conclusion

Ferritin and transferrin saturation are complementary markers whose interpretation changes with clinical context. Early diagnosis depends on recognizing deficiency before the blood count becomes characteristic and on investigating the cause alongside replacement.

Modern treatment should favor a tolerable regimen, a justified route of administration, and an explicit response assessment. Persistent or recurrent anemia is a diagnostic signal that requires reassessment rather than indefinite repetition of the same prescription.

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