

## CLINICAL VIGNETTE

# Evaluation of Iron Deficiency Anemia in a Premenopausal Woman

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Iron deficiency anemia, one of the most common disorders in benign hematology has diverse causes and calls for careful evaluation. We present a typical case of IDA in a premenopausal woman and briefly discuss the symptoms, causes, diagnosis, and treatment of IDA.

### *Case Presentation*

A 42-year-old woman with no significant past medical history was referred for Iron Deficiency Anemia (IDA) two years ago. She noted fatigue, ice craving and pica. The etiology of her IDA was heavy menstrual bleeding and her gynecologist prescribed oral iron and oral contraceptive pills. However, she was intolerant to both agents due to nausea, leading up to referral to hematology. Her initial hemoglobin, iron saturation, and ferritin measurements were 8.0 g/dL, 5%, and 10 ng/mL. She was treated with intravenous iron (ferumoxytol, two doses of 510 mg one week apart), with improvements in all her labs as well as resolution of her symptoms. Currently, her condition is well managed with the intravenous iron “maintenance” every six months or so.

### *Iron Deficiency Anemia and Symptoms*

IDA comprises about 50% of anemia cases and is the most common nutritional disorder globally.<sup>1</sup> Pallor, fatigue, dyspnea, and headaches are common symptoms of IDA. More rarely, patients may have alopecia, atrophic glossitis, pica, restless leg syndrome, dry and damaged hair, tachycardia, cardiac murmur and neurocognitive dysfunction.<sup>1,2</sup>

### *Causes*

IDA should not be considered a final diagnosis but as a symptom of an underlying condition that needs thorough investigation.<sup>3</sup> Causes of IDA can be categorized as: increased iron requirements, insufficient iron intake, malabsorption, chronic blood loss, and related to anemia of chronic disease (ACD).<sup>4</sup> In developed countries, heavy or irregular menstrual bleeding, affects 9–14% of all menstruating women and is a common cause of IDA.<sup>1</sup> Middle-aged or older men and postmenopausal women diagnosed with IDA should be evaluated with upper endoscopy and/or colonoscopy to assess for gastrointestinal (GI) sources of bleeding, which may be due to G.I. malignancies especially in older patients.<sup>1,3</sup> A study of

patients with IDA of unknown origin found 11% with new G.I. cancers.<sup>1</sup> Celiac serology should be examined in all adults presenting with IDA. When the serologic testing is positive, upper endoscopy with duodenal biopsies is indicated to confirm the diagnosis and assesses additional etiologies.<sup>1</sup> Bariatric surgery has emerged as a significant cause of IDA, and the incidence of post-op IDA can be as high as 50%.<sup>5</sup> The duodenum is the primary site of iron absorption and surgeries bypassing the duodenum are associated with a higher incidence of IDA. Iron deficiency is found as a sequela of most types of bariatric surgeries.<sup>5</sup>

### *Diagnosis*

Although IDA is the most prominent cause of microcytic anemia, defined as mean corpuscular volume, MCV, <80 fL up to 40% of patients with IDA have normal MCV. Thus, iron deficiency should be considered in all cases of anemia, regardless of MCV.<sup>1</sup> Increased total iron-binding capacity, decreased serum iron, and reduced transferrin (TF) saturation may be present as IDA.<sup>3</sup> The most accurate test to diagnose IDA may be ferritin, which reflects iron storage.<sup>1</sup> Although ferritin levels below 15 mg/L define diagnosis of IDA, using a cutoff of 30 mg/L improves sensitivity and specificity.<sup>1</sup> Of note, ferritin is an acute-phase reactant and can be elevated in patients with chronic inflammation or infection, masking the IDA diagnosis.<sup>1</sup> Therefore, ferritin thresholds below 100 mg/L or even higher values, combined with low (<20%) TF saturation, are recommended to improve accuracy in diagnosing iron deficiency, in the presence of inflammatory morbidities.<sup>4</sup> Serum ferritin is the best equivalence to the bone marrow’s stainable iron stores in the absence of inflammation or infection and is regarded as the gold standard in evaluating exhausted iron stores.<sup>4</sup> TF saturation (<16%) and hepcidin levels, which are minute in absolute iron deficiency, are not essential to establish diagnosis of IDA.<sup>4</sup>

### *Treatment*

The treatment goal is to replete the abnormally low iron stores to normalize hemoglobin concentrations, thereby relieving symptoms and improving quality of life.<sup>2</sup> Oral iron supplementation, the usual first-line therapy often mandated by health insurance, and intravenous iron infusion are the two main therapeutic options.<sup>1,3</sup>

Oral iron salts, including iron sulfate, fumarate, and gluconate, are used to treat absolute iron deficiency. Oral iron salts, including iron sulfate, fumarate, and gluconate, are used to treat absolute iron deficiency with ferrous sulfate being the gold standard.<sup>2,4,6</sup> Growing evidence suggests low doses are more effective and better tolerated than the conventionally recommended 100–200 mg of elementary iron per day. When given in divided doses, a total of 60 mg per day is recommended.<sup>4,6</sup> When taking oral iron 30%–70% of patients experience GI side effects such as nausea, dyspepsia, constipation, diarrhea, and metallic taste. Thus, oral iron may have poor adherence, compromising the three to six months anticipated treatment needed to replete iron stores.<sup>6–8</sup> Although iron is more readily absorbed when taken on an empty stomach, it can be taken with meals when GI upset occurs, with absorption decreased to 40%. Increased patient adherence may be offset by inferior absorption.<sup>2,3,7</sup> Other ways to decrease GI side effects are by taking smaller doses of iron between meals and at bedtime or by changing ferrous sulfate to ferrous gluconate.<sup>2</sup> There is interest in compounds better tolerated than iron salts; and many candidates have been suggested. These include sucrosomial iron, heme iron polypeptide, and iron-containing nanoparticles. However, studies on these alternatives are limited.<sup>4</sup> GI absorption of elemental iron is enhanced in the presence of an acidic gastric environment. Iron absorption is decreased when gastric acid is inhibited by antacids, H2 blockers, and proton pump inhibitors and can be increased by the simultaneous intake of ascorbic acid.<sup>3,6</sup> Additionally, ascorbic acid can block calcium and fiber's negative effect on iron absorption, improving the bioavailability of dietary iron.<sup>7</sup> Foods rich in tannates such as coffee, tea or phytates such as bran, cereal could reduce iron absorption and should be avoided near the time of iron ingestion.<sup>3</sup>

Indications for IV iron include blood loss that surpasses the absorptive capacity for oral iron, iron malabsorption cases, and failed or poorly tolerated oral treatment.<sup>2</sup> Frequently used IV iron agents are iron gluconate, iron sucrose, ferric carboxymaltose, ferumoxytol, low molecular weight iron dextran, and iron isomaltoside.<sup>4</sup> They rarely cause severe hypersensitivity reactions.<sup>6</sup> IV iron therapy is contraindicated during the periods of active infection since iron may be a growth factor for several pathogens. An ongoing controversy centers around whether there is a risk of infection after IV iron.<sup>4</sup> Currently used IV iron formulations are equally safe and effective, with rapid effects and little GI toxicity. Studies have demonstrated both better tolerance and a superior efficacy over oral iron.<sup>4,8</sup>

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