

# Gastrointestinal Evaluation for Premenopausal Women with Iron Deficiency Anemia: What Is Appropriate?

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Iron deficiency anemia is by far the most common form of anemia in the world. In the United States alone, it has been estimated that approximately 11% of women aged 20 to 49 are iron deficient and 5%, or 3.3 million, have iron deficiency anemia (1). Among adults, women in their reproductive years are most susceptible to iron depletion and iron deficiency anemia because of menstrual blood loss and pregnancy-associated requirements. In groups other than premenopausal women, not only is iron deficiency anemia much less common, but it has traditionally been assumed to arise from gastrointestinal blood loss. Thus, the standard of care for men and postmenopausal women with iron deficiency anemia has been to perform gastrointestinal evaluation to exclude gastrointestinal tract pathology (2,3). In contrast, iron deficiency anemia in most premenopausal women is generally managed by simple iron supplementation, and gastrointestinal evaluation is usually not performed.

Iron, as the core element of the hemoglobin molecule, is one of the most important elements in the body. Accordingly, an efficient system of conserving and recycling it has evolved. Normal iron homeostasis is tightly controlled depending on the body's requirements. Under normal conditions, nearly 1 mg iron is lost from the gastrointestinal tract via intestinal cell sloughing and minute amounts of bleeding each day; this loss is offset by precisely an equivalent amount of iron absorption. In states of excess iron loss, whether from the gastrointestinal tract, or from extra-gastrointestinal sites, iron absorption can increase by a factor of twofold to threefold. However, iron absorption and homeostasis may be affected by the amount of iron in the diet or intrinsic diseases of the gastrointestinal tract, such as atrophic gastritis, that impair iron absorption and can even contribute to primary iron imbalance (4). Iron deficiency anemia is the simple result of greater iron loss than absorption.

From menarche to menopause, iron metabolism in women is governed by predictable iron loss during men-

struation and pregnancy. Average blood loss for normal women of childbearing age during menstruation is approximately 45 mL (5), which represents nearly 30 mg iron; this amount is at least 38% of the total iron loss for women not taking oral contraceptives or with menorrhagia/menometrorrhagia (6). Such blood loss requires a compensatory increase in absorption. However, when iron requirements are greater than 1.6 to 1.8 mg per day (and iron is not supplemented), iron depletion and ultimately iron deficiency anemia ensue (6). Women with iron deficiency anemia are more likely to have higher than normal menstrual losses, and moreover, a substantial proportion of menstruating women with iron deficiency anemia underestimate their menstrual blood loss (7,8). Further, during pregnancy, an additional 900 mg of iron is required to support the fetus and expanded erythrocyte mass; the prevalence of iron deficiency anemia during the third trimester ranges from 12% to 38% (9,10). Thus, it can be readily appreciated why iron deficiency anemia is so common in premenopausal women.

In any patient, including menstruating women, many gastrointestinal tract lesions can lead to chronic blood loss and iron deficiency anemia. The mechanism of gastrointestinal bleeding usually entails mucosal injury with epithelial cell disruption. A lesion consistent with chronic gastrointestinal bleeding can be identified in up to two thirds of patients with iron deficiency anemia (11–14). The most common causes of gastrointestinal blood loss leading to iron deficiency include severe ulcerative processes of the upper gastrointestinal tract as well as colonic or gastric carcinoma, each of which can bleed enough to cause an iron deficient state (11–15).

In this issue of the *Journal*, a study by Bini and coworkers (16) raises the possibility that gastrointestinal tract lesions account for iron deficiency anemia in some premenopausal women. This retrospective study reviewed the results of colonoscopy, esophagogastroduodenoscopy, and small bowel radiographs in 186 patients referred for gastrointestinal evaluation over a 5-year period at an academic institution (colonoscopy and esophagogastroduodenoscopy were performed in all patients; upper gastrointestinal series with small bowel follow-through was performed in 75% of those with negative endoscopies). The retrospective design is a methodological limitation of the study, particularly if we are to con-

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sider generalizing this report to our own practices: since gastrointestinal evaluation of premenopausal women with iron deficiency anemia has not generally been considered to be standard of care, the possibility of selection bias must be considered. We are not told about the total number of premenopausal women with iron deficiency anemia, including those who did not undergo gastrointestinal evaluation, seen in the institution over the 5-year study period. Certainly, it is unlikely that all or even most premenopausal women with iron deficiency anemia were referred for gastrointestinal tract evaluation.

This important concern notwithstanding, the results reported in the cohort of 186 patients referred for evaluation were remarkable. A total of 23 patients (12%) were found to have gastrointestinal tract abnormalities, including mass lesions, ulceration or severe mucosal inflammation, of which nearly half were malignant. Lesions were identified as commonly in the upper gastrointestinal tract as in the colon, as has been demonstrated in other studies. All 8 patients with fecal occult blood and gastrointestinal symptoms had gastrointestinal tract lesions identified. Additionally, the rate of identification of gastrointestinal tract lesions was higher in asymptomatic patients with fecal occult blood than in those without fecal occult blood, although the difference was not statistically significant. Of the 109 patients without fecal occult blood or gastrointestinal symptoms, 7 patients (7%) had lesions (including 2 with gastric and 1 with colonic cancer) compared with 16 of 79 (22%) with fecal occult blood or gastrointestinal symptoms. Overall, patients with fecal occult blood, severe anemia (hemoglobin <10 g/dL), or abdominal symptoms were most likely to have a lesion identified.

Based on the data presented by Bini and coworkers, should all 3.3 million women in the United States (and the many millions outside this country) with iron deficiency anemia undergo gastrointestinal tract evaluation? The answer to this question is unknown, but likely to vary for each patient. For those with fecal occult blood (the presence of which should be tested for in all patients with iron deficiency anemia), severe anemia, gastrointestinal symptoms or weight loss, the answer is almost certainly, yes, evaluation is indicated. For asymptomatic women or those with menorrhagia or menometrorrhagia, the answer is less clear. In this latter group, a reasonable approach is to try to quantitate any menstrual abnormality and judge how likely this might be to cause iron deficiency. Additionally, any compliant patient failing a trial of iron therapy should probably undergo gastrointestinal evaluation. However, we do not currently know whether the cost and risk of gastrointestinal investigation in asymptomatic premenopausal women with iron deficiency anemia is offset by the potential benefit of finding gastrointestinal tract lesions.

Although it is clearly important to focus on the gastro-

intestinal tract as a source of potential bleeding lesions in patients with iron deficiency anemia, it is also critical to recognize that iron deficiency anemia is multifactorial in etiology. This is particularly true for women of child-bearing age, since extra-gastrointestinal blood loss is often obligatory. The data provided by Bini and coworkers provide a rational basis to perform gastrointestinal tract evaluation in certain subgroups of premenopausal women with iron deficiency anemia. However, their results are insufficient to recommend that all premenopausal women with iron deficiency anemia undergo routine endoscopic evaluation. Rather, these data should provide the impetus for further study so that we can better understand which subgroups of premenopausal women with iron deficiency anemia require gastrointestinal evaluation.

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