

# The Role of Endoscopy in the Evaluation of Iron Deficiency Anemia in Premenopausal Women

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## Abstract

**Background:** Men and postmenopausal women with iron deficiency anemia are routinely evaluated to exclude a gastrointestinal source of suspected internal bleeding. Iron deficiency anemia in premenopausal women is often treated with simple iron replacement under the assumption that the condition is due to excessive menstrual blood loss.

**Objectives:** To determine the yield of endoscopy evaluations in premenopausal women with iron deficiency anemia.

**Methods:** Upper and lower gastrointestinal endoscopic examinations were conducted in 45 premenopausal women with iron deficiency anemia not related to gynecologic or nutritional causes.

**Results:** Forty-three of the 45 women fulfilled the entry criteria and were enrolled. Their mean age was  $35 \pm 15$  years and their mean hemoglobin level  $9.3 \pm 2.3$  g/dl. Twenty-eight upper gastrointestinal lesions were demonstrated in 24 of the 43 patients (55.8%): erosive gastritis in 12 (27.9%), erosive duodenitis in 4 (9.3%), erosive esophagitis in 3 (7.0%), hiatus hernia (with Cameron lesions) in 3 (7.0%), active duodenal ulcer in 1 (2.3%) and hyperplastic polyp (10 mm) in 1 (2.3%). Five lower gastrointestinal lesions were detected in 5 patients (16.3%): 2 (4.6%) had adenocarcinoma of the right colon, 2 (4.6%) had pedunculate adenomatous polyp > 10 mm, and 1 (2.3%) had segmental colitis (Crohn's disease). One patient (2.3%) had pathologic findings in both the upper and lower gastrointestinal tracts.

**Conclusions:** Our findings of a gastrointestinal source of chronic blood loss in 28 of 43 premenopausal women with iron deficiency anemia (65.1%) suggest that this population will benefit from bi-directional endoscopic evaluation of the gastrointestinal tract.

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Endoscopists are often asked to evaluate iron deficiency anemia and to identify the source of bleeding. There are sparse data available on the yield of gastrointestinal investigations in premenopausal women with IDA [1-6]. In the United States, 5-11% of premenopausal women and 1-4% of men are iron deficient, and approximately 5% and 2% of them, respectively, have IDA [7]. Iron deficiency is most commonly found in women during their reproductive years because of iron loss associated with menstruation and pregnancy [8]. Iron deficiency in other populations is traditionally considered to be the result of chronic occult gastrointestinal bleeding and/or dietary deficiency. Thus, the standard diagnostic procedure for men and

postmenopausal women with iron deficiency is to investigate gastrointestinal tract pathology as well as rule out a nutritional cause [8,9].

Menstrual blood loss (especially menorrhagia), pregnancy, and breast-feeding are usually responsible for IDA in premenopausal women. Self-reported quantification of menstrual loss has been shown to be unreliable, even though pictorial blood loss assessment charts have been shown to have a sensitivity and specificity of around 80% for detecting menorrhagia [1]. In general, premenopausal women with IDA are likely to be treated with iron supplements, and attempts are made to mitigate potential causes of iron deficiency (e.g., menorrhagia, poor diet). In contrast, the standard protocol for diagnosing IDA among men and postmenopausal women is to exclude a gastrointestinal source of bleeding. The standard gastrointestinal methods for evaluating the presence of IDA are endoscopic (esophago-gastro-duodenoscopy and colonoscopy) and/or radiographic (air-contrast barium enema and upper gastrointestinal series) [9-14].

According to a few recently published papers [2-6], a gastrointestinal source of chronic blood loss was identified in a substantial proportion of premenopausal women with IDA [8,11,12]. Even though the studies dealing with this important subject are few in number, it was recommended that gastrointestinal investigations of these women be carried out according to the same guidelines as those used in other patient populations [8,11,12].

The current study was conducted on premenopausal women who were referred to the gastroenterology unit for evaluation after excluding all other possible causes of their IDA (hematologic, nutritional, gynecologic, non-steroidal anti-inflammatory drug use, etc). Its aim was to evaluate the diagnostic yield of gastrointestinal studies and identify the various pathologies of the upper and lower tract in cases where it was discovered to be the source of IDA.

## Patients and Methods

From January 1999 through December 2003, a total of 1926 women suffering from IDA underwent bi-directional EGD and/or colonoscopy studies. Forty-five of them (2.3%) were premenopausal and comprised the study group. Patients with confirmed gynecologic or nutritional causes of IDA were excluded. Each patient underwent a complete workup to exclude other sources, including hematologic, nutritional, gynecologic (menorrhagia),

IDA = iron deficiency anemia

EGD = esophago-gastro-duodenoscopy

overt gastrointestinal bleeding, pregnancy, gastrointestinal surgery, abnormal menstruation, and the use of NSAIDs during the 3 months prior to entering the study. IDA was defined as a hemoglobin level < 11 g/dl, serum iron level < 50 µg/dl and total iron-binding capacity level > 300 µg/dl. Since most ferritin levels were not available, they were not included in the analysis. We retrospectively reviewed the medical and laboratory data, including endoscopic and pathologic reports of the entire study group.

All study participants underwent upper and lower endoscopic studies, but only 10 patients had serology testing (anti-tissue transglutaminase antibodies) prior to the endoscopic evaluation, and in 37 patients a small bowel biopsy was taken to rule out celiac disease. Patients whose upper endoscopic studies showed evidence of peptic disease underwent rapid urease test (CLO test). Data on all endoscopic abnormalities were retrieved from our computerized database. Those abnormalities considered as possible causes of upper gastrointestinal lesions were erosive esophagitis, esophageal ulcer, esophageal tumor, hiatus hernia (with Cameron lesions), erosive/hemorrhagic gastritis, polyps (> 1 cm) with erosion, gastric ulcer and gastric tumor. The lower gastrointestinal tract lesions regarded as possible causes of IDA included colorectal cancer, angiodysplasia, colorectal polyp (> 1 cm) and colitis. Double (bi-directional) endoscopy was performed in each patient. The procedure was done using either a Fujinon EC 20HR2 (Germany) or a Pentax EG 2901 video-endoscopy Pentax EC 3801L (Asahi Optical, Japan). Both procedures were usually performed on the same day, and the patients signed an informed consent. Seven of the women were evaluated as inpatients.

## Statistics

Statistical analyses were carried out with Student's *t*-test and significance was set at  $P < 0.05$ .

## Results

Of the 45 women who were originally enrolled in the study 2 were excluded because they had undergone only one of the endoscopic studies. The mean age of the study cohort was  $35 \pm 15$  years (range 18–50) and their mean hemoglobin level was  $9.3 \pm 2.3$  g/dl (range 4–11). Twenty-eight upper gastrointestinal lesions were detected in 24 patients (55.8%) as follows: erosive gastritis in 12 (27.9%) (positive urease test in 10 of them), erosive duodenitis in 4 (9.3%) (positive urease test in all 4), erosive esophagitis in 3 (7.0%), hiatus hernia (with Cameron lesions) in 3 (7.0%), active duodenal ulcer in 1 (2.3%) (her urease test was positive) and hyperplastic polyp (10 mm) in 1 (2.3%). Five lower gastrointestinal lesions were detected in 5 patients (16.3%): 2 (4.6%) had adenocarcinoma of the right colon, 2 (4.6%) had pedunculate adenomatous polyp > 10 mm (the polyps were endoscopically resected), and 1 (2.3%) had segmental colitis (Crohn's disease). Neither patient with adenocarcinoma

NSAIDs = non-steroidal anti-inflammatory drugs

TTG = tissue transglutaminase

**Table 1.** Pathologic findings and hemoglobin levels of the 43 study patients\*

	Hemoglobin <10 g/dl	Hemoglobin > 10 g/dl
Erosive gastritis	3	9
Erosive duodenitis	1	3
Erosive esophagitis	2	1
Hiatus hernia (with Cameron lesions)	1	2
Gastric polyp	1	0
Duodenal ulcer	1	0
Celiac disease	1	3
Adenocarcinoma of the colon	2	0
Adenomatous polyp	2	0
Crohn's disease	1	0

\* Some patients had more than one lesion

of the colon had a known family history of a first-degree relative with colorectal tumor. One patient (2.3%) had both upper and lower gastrointestinal tract pathology. Only 37 patients underwent small bowel biopsy: 4 of them had pathologic findings compatible with celiac disease and the findings of the other 33 showed normal small bowel histology, while only 1 of the 10 patients who had undergone serology testing (anti-TTG) prior to the endoscopic evaluation had a positive result (correlating to the findings on small bowel biopsy).

Most of the patients (38/43) had no gastrointestinal symptoms. Twenty-nine (67.4%) had an upper or lower source of gastrointestinal bleeding, leaving 14 (32.6%) premenopausal women with IDA whose gastrointestinal tract was ruled out as the source of bleeding.

We divided the study group into two subgroups according to the severity of the anemia, i.e., a hemoglobin level higher or lower than 10 g/dl [Table 1]. We considered cases with hemoglobin >10 g/dl to be less serious. We also divided them by age, i.e., under and over 40 years. There were no significant differences between the findings in these groups ( $P < 0.05$ ).

EGD and colonoscopy detected a total of 29 pertinent findings in 28/43 patients (65.1%). There were four additional patients with serologic and biopsy evidence for celiac disease. Of these 33 pathologic findings, 20 lesions were in patients above 40 years of age. Two-thirds of the 28 patients who had significant findings (cancer, colitis, adenomatous polyp and reflux esophagitis) were above 40 years old.

## Discussion

Chronic occult blood loss from the gastrointestinal tract is widely accepted as a major cause of IDA. Obscure gastrointestinal bleeding afflicts at least 10% of the population, and while endoscopists are often asked to evaluate these patients and to identify the source of bleeding [7,9,13–15], the existing guidelines for evaluating IDA patients refer largely to patients older than 50 [8,12]. There are sparse data on gastrointestinal investigations in premenopausal women who have IDA, but significant gastrointestinal pathology was detected in published studies [2,4–6]. Women who menstruate regularly represent a

large otherwise healthy population in which IDA is common, with a prevalence of 5–10% [1,7].

Iron deficiency is most commonly found in women during their reproductive years because of menstrual and pregnancy-associated iron loss [1]. In other populations, iron deficiency has traditionally been considered the result of chronic occult gastrointestinal bleeding and/or dietary deficiency. Thus, the standard procedure for investigating the source of IDA among men and postmenopausal women is to rule out gastrointestinal tract pathology and a nutritional cause [10–14]. As a result, celiac disease in anemic premenstrual women often goes undetected and is under-investigated, yet it occurs in more than 1% of them [16]. In the present study, we found 4 cases of celiac disease among the 37 women who underwent small bowel biopsy.

A comparison of our findings with those of recently published papers [2,4–6] reveals that the percentage of pathologic lesions in the upper gastrointestinal tract varies considerably, from 13 to 55%. This wide range may result from the other investigators' inclusion of patients taking NSAIDs. Our findings and those of other studies [2,4] on the lower gastrointestinal tract, however, are quite similar (i.e., a range of 7 to 14%), as are the percentages of significant pathologic findings (~3%) [2,4]. In a recent study of 3546 women with IDA, Olofinlade et al. [17] found that 61 (1.63%) had colorectal cancer. These investigators suggested that this cancer occurs predominantly in women of childbearing age and that they tend to present with late-stage disease compared to young males. This observation was not confirmed by our group or by others [2,4].

We found no correlation between the presence of pathology and gastrointestinal symptoms. The majority of our patients were asymptomatic, as reported by Bini et al. [4], but not by others [2,5,6]. Specifically, the women in our study described symptoms related to apparent anemia (fatigue and weakness) and not those characteristic of gastrointestinal pathology.

In one of the largest published studies on gastrointestinal endoscopic evaluation of premenopausal women, Nahon and co-workers [6] found that a significant percentage (10/241, 4%) had both upper and lower gastrointestinal lesions, a figure similar to ours (1/43, 2.3%). Based on these data and on our experience with elderly patients [14,15], we recommend that bi-directional endoscopies, routine small bowel biopsies and/or celiac serology be considered for this younger population as well.

In conclusion, our results show that gastrointestinal sources of chronic blood loss exist in a significant proportion of premenopausal women with IDA and that their IDA should not be attributed solely to menstrual blood loss. This younger population can benefit from the more comprehensive diagnostic protocol traditionally reserved for men and postmenopausal women.

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