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Letter to Editor (Pages: 243-245)

Iron Deficiency Anemia in Infants Receiving Proton Pump Inhibitors or Histamine-2 Receptor Antagonists for Reflux: Evidence and Uncertainties

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Abstract

The effect of pharmacological acid suppression on iron status in infants remains uncertain. Although reduced gastric acidity may impair non-heme iron absorption, evidence is insufficient to establish the prevalence of iron deficiency anemia among infants receiving proton pump inhibitors or histamine-2 receptor antagonists. Reliance on hemoglobin without assessing iron stores, underrepresentation of certain drug classes, and inadequate control of nutritional factors limit interpretation. The absence of a statistically significant increase in anemia does not exclude iron deficiency. Distinguishing treatment effects from disease-related mucosal injury and feeding difficulties further complicates assessment. This letter emphasizes the distinction between iron deficiency and iron deficiency anemia, cautions against extrapolating adult findings to infants, and supports indication-based prescribing. Prospective studies incorporating baseline and follow-up assessments of iron status, detailed drug exposure and dietary data, and adjustment for disease severity are needed. Meanwhile, clinical decisions should balance treatment benefits against uncertainty regarding nutritional outcomes.

Key Words: Iron deficiency anemia, Infant, Histamine-2 receptor antagonists, Gastroesophageal reflux, Proton pump inhibitors.

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Dear Editor,

Assessing the safety of acid-suppressive treatment in infants requires consideration of potential nutritional consequences beyond reflux symptom control. The joint guidelines of the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition recommend against using proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) for crying, distress, or visible regurgitation in otherwise healthy infants, while recognizing a therapeutic role in reflux-related erosive esophagitis (1). An important question remains: does acid suppression increase the risk of iron deficiency or iron deficiency anemia in infants, and can existing evidence establish the prevalence of these outcomes?

This concern is biologically plausible. Gastric acid facilitates the solubilization and availability of non-heme iron for absorption; reduced acidity may therefore impair iron uptake. In the case–control study by Lam et al., at least two years of PPI use was associated with an adjusted odds ratio of 2.49 for iron deficiency, compared with 1.58 for H2RA use (2). Nevertheless, an observational association does not establish causality. Differences in age, baseline iron stores, feeding patterns, and exposure duration also limit direct extrapolation to infants.

More directly relevant evidence comes from the retrospective cohort study by Abu-Sulb et al. The investigators compared 135 children who had received at least one month of acid-suppressive treatment during infancy with 135 unexposed children. Mean treatment duration was 3.22 months, and hemoglobin was measured at 12–15 months of age. Anemia was identified in 12.6% of exposed children and 11.1% of controls, with no statistically significant difference ($p = 0.706$). Mean hemoglobin concentrations were 11.85 and 11.94 g/dL, respectively, and likewise did not differ significantly ($p = 0.447$) (3).

However, these findings do not fully address the question of iron deficiency anemia. Ferritin and other specific indicators of iron status were not assessed; consequently, the reported proportions represent anemia rather than confirmed iron deficiency anemia. Hemoglobin alone cannot identify depleted iron stores before anemia develops. This distinction is central: failure to detect an increase in anemia does not necessarily exclude an adverse effect on iron status.

The distribution of drug exposure further limits interpretation. Ranitidine was prescribed to 91.1% of exposed children, whereas relatively few received PPIs (3). The study therefore provides limited evidence for comparing drug classes or excluding a PPI-specific effect. Hemoglobin measurement after treatment discontinuation in many children, together with insufficient information on pretreatment iron status and nutritional intake, introduces additional uncertainty. A nonsignificant difference under these conditions should not be interpreted as evidence of equivalence or definitive safety.

Separating treatment effects from disease effects presents another challenge. In a study of 172 children with reflux diagnosed by esophageal pH monitoring, Lupu et al. identified anemia in 23 children and reported findings linking reflux with reduced serum iron (4). This study neither establishes an effect of acid-suppressive medication nor specifically addresses infants. Nevertheless, it highlights the need to consider disease-related explanations rather than attributing anemia in treated patients solely to medication. Mucosal injury and potential iron loss warrant consideration alongside drug exposure. Disease severity may influence both treatment selection and hematological outcomes, creating confounding by indication.

In Iran, the background burden of iron deficiency strengthens the relevance of this question. A meta-analysis by Nazari et al. estimated pooled prevalences of 27.7% for iron deficiency and 18.2% for iron deficiency anemia among children younger than six years; the latter estimate had a 95% confidence interval of 14.3–22.0% (5). These estimates are not specific to infants receiving reflux treatment and derive from studies conducted across different periods and settings. They should therefore not be interpreted as current national estimates or used to quantify medication-associated risk.

Direct comparison of the 18.2% estimate with the 12.6% anemia prevalence among exposed children in the American cohort would also be inappropriate because the age groups, outcome definitions, and

sampling methods differ (3,5). A more informative comparison concerns the scope of the evidence: Iranian data describe the background burden of iron deficiency, whereas the American cohort examines medication exposure without assessing iron stores. The Iranian trial by Azizollahi and Rafeey compared omeprazole and ranitidine in 60 infants over two weeks but focused on symptom changes rather than iron status (6). Ranitidine is discussed here solely as a historical study exposure, not as a treatment recommendation.

Addressing this evidence gap requires a prospective, multicenter cohort enrolling infants with clearly documented treatment indications before medication initiation. Iron status should be assessed before, during, and after exposure using hemoglobin, red-cell indices, and ferritin interpreted alongside inflammatory markers. Drug type, dose, duration, feeding pattern, prematurity, birth weight, and actual iron supplement intake should be recorded. Comparison groups should have similar disease severity and nutritional characteristics to reduce confounding by indication. Iron deficiency without anemia, confirmed iron deficiency anemia, and anemia attributable to other causes should be reported separately, with effect estimates and confidence intervals.

Clinically, uncertainty justifies neither withholding necessary treatment nor prescribing without a clear indication. Confirming the indication and reassessing the need for continued therapy are consistent with reflux guidelines (1). Conversely, the evidence discussed here is insufficient to justify a uniform laboratory monitoring schedule for all treated infants or routine preference for newer iron formulations. Assessment should reflect individual clinical circumstances and nutritional risk, while the need for, and timing of, monitoring specifically related to acid-suppressive treatment remain research questions.

CONCLUSION

Current evidence is insufficient to establish the prevalence of iron deficiency anemia in infants receiving PPIs or H2RAs. The directly relevant cohort found no significant increase in anemia, but the absence of iron-store assessment and predominance of ranitidine exposure limit conclusions regarding iron deficiency or PPI-specific risk. The background burden of iron deficiency in Iran reinforces the need for research rather than demonstrating medication-related harm. Indication-based prescribing and prospective studies that distinguish disease-related, nutritional, and treatment effects provide a sound basis for more informed clinical decisions.

CONFLICT OF INTEREST: None.

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