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Empirical Iron Prescribing in Children with Anemia: Limitations in Populations with a High Prevalence of Thalassemia

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Abstract,

Microcytic hypochromic anemia is common in children, and iron deficiency is its most frequent cause. However, in regions with a high prevalence of thalassemia, including Iran, microcytosis and mild anemia are not necessarily attributable to iron deficiency. Carriers of alpha- or beta-thalassemia may also present with low mean corpuscular volume (MCV), low mean corpuscular hemoglobin (MCH), and mild anemia. Empirical iron prescribing without appropriate diagnostic evaluation may result in ineffective treatment, gastrointestinal adverse effects, delayed recognition of hemoglobinopathies, and missed opportunities for genetic counseling. The Mentzer index, red cell distribution width (RDW), serum ferritin, and C-reactive protein (CRP), particularly in the presence of inflammation, can assist in differentiating iron deficiency anemia from thalassemia trait. Population-based iron supplementation remains important, particularly for infants aged 6–23 months; however, therapeutic iron should be prescribed after assessment of iron status and consideration of possible thalassemia.

***Key Words**:* Beta-thalassemia minor, Children, Empirical iron therapy, Iran, Iron deficiency anemia.

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Dear Editor,

Microcytic hypochromic anemia is one of the most common problems in pediatrics and primary care, and iron deficiency is its most frequent cause (1). The World Health Organization recommends daily iron supplementation for infants and children aged 6–23 months in settings where anemia prevalence in this age group is 40% or higher (2). This intervention forms an important component of anemia-prevention programs in many low- and middle-income countries, particularly in sub-Saharan Africa and South Asia, where iron deficiency, recurrent infections, parasitic diseases, and limited access to iron-rich foods commonly coexist (2, 3). In Iran, iron deficiency also remains an important clinical and public health problem; a systematic review and meta-analysis estimated the prevalence of iron deficiency anemia among Iranian children under six years of age to be approximately 18.2% (4). Nevertheless, empirical iron prescribing for every child with microcytic anemia—particularly in populations with a high prevalence of thalassemia—requires re-evaluation.

Microcytic hypochromic anemia may result from iron deficiency, alpha- or beta-thalassemia trait, anemia of chronic disease, lead poisoning, and less common disorders (1, 5). In iron deficiency, the red blood cell count is usually reduced, whereas in thalassemia carriers it is often normal or increased (1, 5). The Mentzer index—defined as the ratio of MCV to the red blood cell count—may help differentiate thalassemia trait from iron deficiency: values below 13 favor thalassemia trait, whereas values above 13 favor iron deficiency (1, 5). Because of its simplicity and low cost, this index is a useful screening tool; however, it lacks perfect sensitivity and specificity and should not replace clinical and laboratory evaluation (5, 6). An increased RDW is more consistent with iron deficiency, whereas RDW is usually mildly elevated or near normal in beta-thalassemia trait (1, 5).

Serum ferritin is the best initial test for assessing iron stores; however, its interpretation becomes difficult in the presence of infection or inflammation (6, 7). According to World Health Organization guidance, ferritin levels below 30 µg/L in children with inflammation may indicate iron deficiency, and concurrent measurement of CRP or alpha-1-acid glycoprotein is recommended (7). This issue is particularly relevant in settings with a high burden of infection and inflammation. In developing countries, including Iran, recurrent infections and mild inflammatory conditions can elevate ferritin levels and mask iron deficiency (6, 7). Therefore, prescribing iron based solely on hemoglobin and MCV, without ferritin assessment and, when indicated, an inflammatory marker, may lead to diagnostic error and inadequate treatment.

Iran lies within the thalassemia belt, and hemoglobinopathies are important genetic disorders in the country (8). The prevalence of beta-thalassemia carriers in Iran has been reported to be approximately 4–8% in different studies, with higher rates in some regions (8, 9). Iran's national premarital thalassemia screening program, implemented in 1997, has played an important role in reducing the number of births of children with beta-thalassemia major (9). This experience is comparable with that of countries such as Cyprus, Greece, and Italy, where screening, genetic counseling, and prenatal diagnosis have substantially reduced the birth of affected children (8, 9). In contrast, although thalassemia prevalence has increased in many Northern European and North American countries because of migration, it remains lower than in endemic Mediterranean, Middle Eastern, and South Asian regions. Therefore, diagnostic algorithms that are effective in low-prevalence countries are not necessarily optimal for settings such as Iran.

In this context, many children presenting with mild microcytic anemia may be thalassemia carriers rather than iron deficient. In such children, iron supplementation usually does not improve hemoglobin levels and may lead to unnecessary repeated prescriptions, repeated visits, gastrointestinal adverse effects, and family anxiety. Individuals with thalassemia minor should not receive iron in the absence of concurrent iron deficiency; iron therapy is indicated only when laboratory evidence of iron deficiency is present (5, 10). This principle is especially important in countries with a high prevalence of thalassemia, including Iran, Turkey, India, Pakistan, and Mediterranean countries, because the likelihood of encountering thalassemia carriers in primary care is higher (8, 10).

Thalassemia alone is not an absolute contraindication to iron therapy. If laboratory evidence of concurrent iron deficiency exists, iron treatment is necessary; the main concern is avoiding empirical prescribing without evaluation (5, 10). Moreover, in coexisting iron deficiency and beta-thalassemia trait, severe iron deficiency may reduce HbA2 synthesis and complicate the diagnosis of thalassemia trait. Therefore, children with an inadequate response to iron or suspected thalassemia require reassessment and, when indicated, hemoglobin electrophoresis (5, 8). In children with transfusion-dependent thalassemia, the main risk is iron overload resulting from repeated transfusions; iron therapy is not only ineffective but may also be harmful, and such patients require iron chelation therapy (10, 11).

It is important to distinguish population-based preventive supplementation from individual empirical treatment. Population-based iron supplementation in infants aged 6–23 months, at a dose of 10–12.5 mg elemental iron per day, has sufficient evidence in settings with a high prevalence of anemia (2, 3). This approach has been effective in developing countries and underserved areas. In contrast, in countries with low anemia prevalence and easy access to laboratory testing, treatment is more commonly based on individual assessment and targeted therapy (6, 7). Iran occupies an intermediate position: it needs preventive supplementation, but because of the high prevalence of thalassemia, it should avoid widespread empirical prescribing without evaluation.

A practical approach in primary care could include assessing family history of anemia, thalassemia, or blood transfusion; evaluating complete blood count parameters, including MCV, MCH, red blood cell count, RDW, and peripheral blood smear when available; calculating the Mentzer index as a screening tool; measuring ferritin and, if inflammation is suspected, CRP; and referring suspected cases for hemoglobin electrophoresis (1, 5, 7). Such an approach is consistent with the principle of diagnostic stewardship: targeted use of tests to reach an accurate diagnosis, avoid unnecessary treatment, and reduce hidden costs to the health system.

Empirical iron therapy may produce a relative improvement in hemoglobin in some children with mild iron deficiency, but this response should not be used as the sole basis for diagnosis. In a child with thalassemia trait, continuing iron therapy despite an inadequate response delays accurate diagnosis and deprives the family of appropriate genetic counseling. Conversely, delayed treatment of true iron deficiency is also harmful; iron deficiency can be associated with impaired growth, cognitive performance, physical activity, and quality of life (4, 6). Therefore, the goal is not to reduce iron prescribing, but to ensure that it is informed, targeted, and based on appropriate evaluation.

CONCLUSION

In populations such as Iran, where the prevalence of thalassemia carriers is considerable, empirical iron prescribing for every child with microcytic anemia is an incomplete approach. Preventive iron supplementation in target groups, particularly infants aged 6–23 months, should be maintained. However, iron therapy in an anemic child should be initiated after assessment of ferritin, consideration of inflammatory status, evaluation of red blood cell indices, and, in suspected cases, diagnostic testing for hemoglobinopathies. Educating primary care physicians, integrating thalassemia screening data into child health records, and developing a simple diagnostic pathway for microcytic anemia can reduce inappropriate prescriptions, prevent diagnostic delays, and improve the quality of pediatric care.

CONFLICT OF INTEREST: None.

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