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Iron deficiency anemia: Impact on women's reproductive health

Felice Petraglia, M.D.[a] and Marie Madeleine Dolmans, M.D., Ph.D.[b,c]

[a] Obstetrics and Gynecology, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Careggi Hospital, Florence, Italy; [b] Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium; and [c] Gynecology Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Iron deficiency (ID) and iron deficiency anemia (IDA) are highly prevalent among women across their life span, especially during the reproductive age. An iron-deficient state has been associated with a number of adverse health consequences, affecting all aspects of the physical and emotional well-being of women. Heavy menstrual bleeding, pregnancy state, and the postpartum period are the major causes of ID/IDA. However, despite the high prevalence and the impact on quality of life, ID/IDA among fertile age women remains underdiagnosed and undertreated.

The present Views and Reviews provides an overview on IDA in women's health, describing the background on iron metabolism, heavy menstrual bleeding pathogenetic mechanisms, including a focus on uterine disorders, such as uterine fibroids and adenomyosis. Iron replacement therapies, patient blood management, and treatment options for uterine disorders also are explored. (Fertil Steril® 2022;118:605–6. ©2022 by American Society for Reproductive Medicine.)

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Iron deficiency anemia (IDA) is a global public health problem that affects developed and undeveloped countries, with important consequences on individual health and quality of life with social and economic repercussions. This condition is highly prevalent among women during their reproductive age. Heavy menstrual bleeding (HMB), pregnancy state, and postpartum are the major conditions determining IDA. However, despite the high prevalence and impact on quality of life, IDA among fertile age women remains underdiagnosed and undertreated (1, 2).

An iron-deficient state causes a number of adverse health consequences, affecting all aspects of the physical and emotional well-being of women. Iron is an essential element involved in a variety of vital functions, including oxygen transport, deoxyribonucleic acid synthesis, metabolic energy, and cellular respiration (2). Iron homeostasis is the result of balanced cooperation between functional compartments (erythroid and proliferating cells), uptake and recycling systems (enterocytes and splenic macrophages), and storage elements (hepatocytes). So far, iron deficiency (ID) and IDA are used to refer to similar conditions. They each carry their own independent risks and, therefore, deserve individual attention. In fact, anemia will appear as the ID continues untreated. Absolute ID is defined as the reduction of total body iron storage (mostly in macrophages and hepatocytes) with subsequent deficient iron supply to tissues. Low hemoglobin defines anemia. Serum ferritin correlates with iron storage (in absence of inflammatory conditions), whereas the iron saturation of serum transferrin is a major indicator of systemic iron homeostasis (2).

Among women of childbearing age, the prevalence of anemia globally is estimated at 30% and, in this sense, women constitute a particularly vulnerable group, since the prevalence and severity of this disease are greater than those described for men worldwide. Women are particularly vulnerable to IDA causing a high symptom burden and disability. The identification of causes of ID/IDA is pivotal and an early diagnosis of ID before the onset IDA is crucial to provide an appropriate treatment (1–3).

The causes of anemia in young women are varied and can be multifactorial. However, the most prevalent cause is absolute ID and among fertile age women, HMB, defined as an excessive menstrual blood loss that interferes with a woman's quality of life, is the leading cause of ID (4). Heavy menstrual bleeding frequently is underreported and a relevant number

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Correspondence: Marie Madeleine Dolmans, M.D., Ph.D., Department of Gynecologie, Université Catholique de Louvain, Avenue Mounier 52, 1200 Brussels, Belgium (E-mail: marie-madeleine.dolmans@uclouvain.be).

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of women are unaware of the condition, as 46% of them have never consulted a doctor for HMB symptoms (3). This may be attributable to inaccurate individual self-perception of HMB and normalization of symptoms. In fact, menstruation is a monthly uterine bleeding, regarded as a sign of reproductive health; however, when characterized by excessive bleeding, it may reflect the presence of uterine disorders (3–5). Endometrial and myometrial mechanisms underlying menstrual bleeding have hormonal, cellular, and molecular components. The exact chronologic order of how the endometrium sheds and repairs is not yet known (4). However, what is known is that the perimenstrual endometrium changes and displays signs of tissue edema, increased endometrial blood flow, vessel permeability, and fragility, as well as a large influx of leucocyte traffic (1). Collectively, this is seen as an inflammatory event and the resolution of inflammation is crucial to limit endometrial injury and control menstrual blood loss. In addition, effective vasoconstriction not only physically reduces the blood flow to the endometrium in the perimenstrual window, thereby reducing menstrual blood loss, it also reduces the amount of oxygenated blood perfusing the endometrium, and therefore, creating a hypoxic environment which in turn underpins tissue remodeling and repair. The final mechanism to control menstrual bleeding is concomitant endometrial repair and regeneration (1).

Heavy menstrual bleeding represents a clinical entity with different structural and nonstructural underlying causes from menarche to menopause, resulting in iron depletion and consequent iron-deficient anemia (5). Uterine fibroids (UFs), adenomyosis, endometrial polyps, cesarean scar defects, and uterine vascular malformations are the main gynecologic causes of IDA in women during reproductive life (3). In 30%–40% of cases, UFs cause a range of symptoms depending on their location and size. The most troublesome complaint necessitating treatment during the reproductive lifespan is HMB, associated or not with pain). The relationship between HMB and UFs remains poorly characterized; however, increased endometrial surface area, the presence of dilated blood vessels on the myoma surface, increased uterine contractility, and peristalsis and changes in expression of potential angiogenic factors seem to represent some of the involved mechanisms (3). In the presence of myometrial causes of HMB, such as UFs or adenomyosis, it is unknown whether aberrations in endometrial function and, thus, the abnormal phenotype of HMB occurs as a result of a primary endometrial disorder, that is, independent of the myometrial cause.

Pregnancy is a physiologic state requiring an increased request of iron and often associated with IDA (2, 4). The most critical situation related to pregnancy is the postpartum hemorrhage, the most common cause of maternal mortality. The patient blood management is the strategic model to prevent and/or treat this critical condition. Patient blood management employs a multidisciplinary and multimodality approach, which provides for timely screening for and treatment of anemia and optimization of hemoglobin level, minimization of blood loss and optimization of hemostasis, and harnessing and optimization of the physiologic adaptation to anemia (2).

The ideal scenario in the 21st century is to assess and treat ID before the emergence of anemia (2). This includes the proper treatment of HMB and the management of ID during all stages of pregnancy. The contributions of UFs, adenomyosis, uterine polyps, and cesarean scar defect in causing HMB should be considered and approached adequately by medical or surgical treatment (3, 5). An effective treatment involves correcting the anemia, correcting the ID and solving their etiologies that may not always be possible. Over time intravenous iron has been and is much more widely adopted and used because of the greater safety profile of the latest generation compounds, their rapid effects and the absence of gastrointestinal toxicity (2).

By implementing this approach, it will result in reducing or avoiding patients' living with years of disabilities. This also will improve quality of life for these women and decrease the large number (40%) of women entering pregnancy with ID. By doing so, it will ensure an optimal fetus development and improve pregnancy outcome, thus avoiding unneeded transfusions (5).

The goal of the present Views and Reviews is to raise awareness among patients and clinicians of the relevance of menstruation-related disorders as a risk for ID and IDA, other than pregnancy and postpartum. A multidisciplinary approach, including the collaboration between general practitioner, gynecologist, and hematologist, is recommended to facilitate a comprehensive and individualized approach to women's care.



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