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Review

Iron deficiency anemia: preconceptional, pregnancy and postpartum management – a call for action

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ABSTRACT

Iron deficiency (ID) and iron deficiency anemia (IDA) are very common in women during their reproductive life, but often these conditions remain unrecognized and left untreated.
Heavy menstrual bleeding (HMB) and pregnancy are associated with ID/IDA, influencing health and the physical and social lives of these individuals. Cross discipline expertise has considered evidence presented here of the pathophysiological mechanisms, the symptoms, the diagnostic criteria and the therapeutic approaches to ID/IDA. A call for action for IDA before and during pregnancy and in the postpartum period is discussed in this review. The uterine disorders causing HMB (which include, but are not limited to uterine fibroids, adenomyosis, endometrial polyps) not only contribute to IDA, but also to infertility and pregnancy complications. It is thus important to reveal and correct ID/IDA. During pregnancy iron requirement increases, thus ID/IDA are common, and these conditions may have a negative impact on pregnancy outcome. Hence, it is critical to early identify and treat ID/IDA during pregnancy with iron replacement therapy. Postpartum IDA may occur following blood loss and major hemorrhage at delivery. In this respect, patient blood management is the best approach for alleviating this critical situation.
Action to increase the awareness for women and physicians on the diagnosis and treatment of ID/IDA is essential to improve health outcomes for women across their life course and for their infants.

Introduction

Iron Deficiency Anemia (IDA) is a global public health problem affecting women during their reproductive years . Despite the high prevalence and impact on quality of life (QoL), IDA among fertile age women is underdiagnosed and consequently undertreated [1,2].

From the data of WHO in 2019, global anaemia prevalence was 29.9% in reproductive age women, equivalent to over half a billion women aged 15–49 years. Prevalence was 29.6% in non-pregnant fertile age women and 36.5% in pregnant women [62].

Heavy menstrual bleeding (HMB), pregnancy itself and postpartum hemorrhage are important causes of iron deficiency (ID) and IDA. Strategies aimed to prevent the development of ID/IDA are required to facilitate diagnosis and management of ID and IDA ideally in pre-conception time, as well as during pregnancy and in the postpartum period [3,4].

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Iron deficiency and iron deficiency anemia

The causes of anemia in young women are diverse and often multifactorial, with the most common being absolute ID. When ID occurs, iron is first drawn from ferritin, its storage form, which is primarily located in the liver. As the deficiency intensifies, iron is also extracted from iron enzymes and iron proteins to support erythropoiesis. This redirection of iron resources towards heme synthesis compromises enzymatic and other vital functions, prior to anemia, which is the final stage of ID manifestation. As a result, ID is linked with a wide range of symptoms that impact mental and physical health as well as work productivity [5]. The symptoms associated with ID alone resemble those of IDA, including fatigue, exhaustion, cognitive impairment, muscle weakness, shortness of breath, dizziness, pica, insomnia, restless legs, and hair loss [6]. Consequently, these conditions underscore the importance of screening for ID in non-pregnant reproductive-aged women by evaluating both ferritin and hemoglobin levels.

ID develops primarily through two mechanisms. These include inadequate iron intake due to diet, restriction or impaired iron absorption, and excessive iron loss because of conditions such as chronic gastrointestinal bleeding and HMB, very often under recognized (Fig. 1) [2,7,8]. ID may be caused also by chronic inflammatory conditions due to autoimmune diseases, cancer and infections [2,9]. Cobalamin or folate deficiency can also be associated with ID, particularly in individuals on vegan and vegetarian diet. In gynecology and obstetrics, bleeding is a common and serious scenario that results in iron loss. Conditions leading to iron loss include HMB, pregnancy and childbirth (either by spontaneous delivery or cesarean section) (Fig. 1). Gynecologists and obstetricians play a crucial role in diagnosing and treating ID and IDA in women, especially those of reproductive age. The ideal approach is to assess and treat ID before the onset of anemia.

IDA is the most frequent type of anemia globally. The treatment of IDA requires teamwork because it is important to detect and treat the cause that led to iron loss in a timely manner and to treat anemia with iron replacement, which can be oral or intravenously. The World Health Organization (WHO) defines anemia as a hemoglobin value of less than 130 g/L for men, and less than 120 g/L for non-pregnanct women (Table 1) [10]. Despite high prevalence of anemia in pregnancy (in nearly 40% of pregnancies according to WHO [11]), there are different definitions of anemia during pregnancy by different major health and gynecological organizations: while the WHO defines anemia as a hemoglobin <110 g/L at any time during pregnancy [12], the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG) define anemia as hemoglobin <110 g/L in the first and third trimesters, and <105 g/L in second trimester [13]. UK guidelines [14] define anemia in pregnancy as a hemoglobin <110 g/L in the first trimester, and <105 g/L in the second and third trimester.

ID can be absolute and functional. Absolute ID refers to the reduction of total body iron stores, due to increased demand, decreased intake, decreased or malabsorption, or chronic blood loss. ì. The most sensitive and reliable test for detecting ID and iron stores in the body is ferritin. Ferritin levels below 30 μg/L represent a diagnostic indicator of absolute ID. Complementary parameters include serum iron, transferrin (which reflects the transport capacity of iron), and transferrin saturation (TSAT), the latter being a significant indicator of available iron for erythropoiesis [61]. Functional ID occurs due to inadequate delivery of iron to the bone marrow despite sufficient reserves (normal or elevated ferritin) in patients with anemia of chronic disease (e.g., in rheumatoid arthritis, systemic lupus, inflammatory bowel disease), in heart failure, or in chronic kidney disease. In the presence of inflammatory conditions, ferritin levels are elevated as it functions as an acute phase reactant protein. Consequently, ferritin levels may primarily reflect the

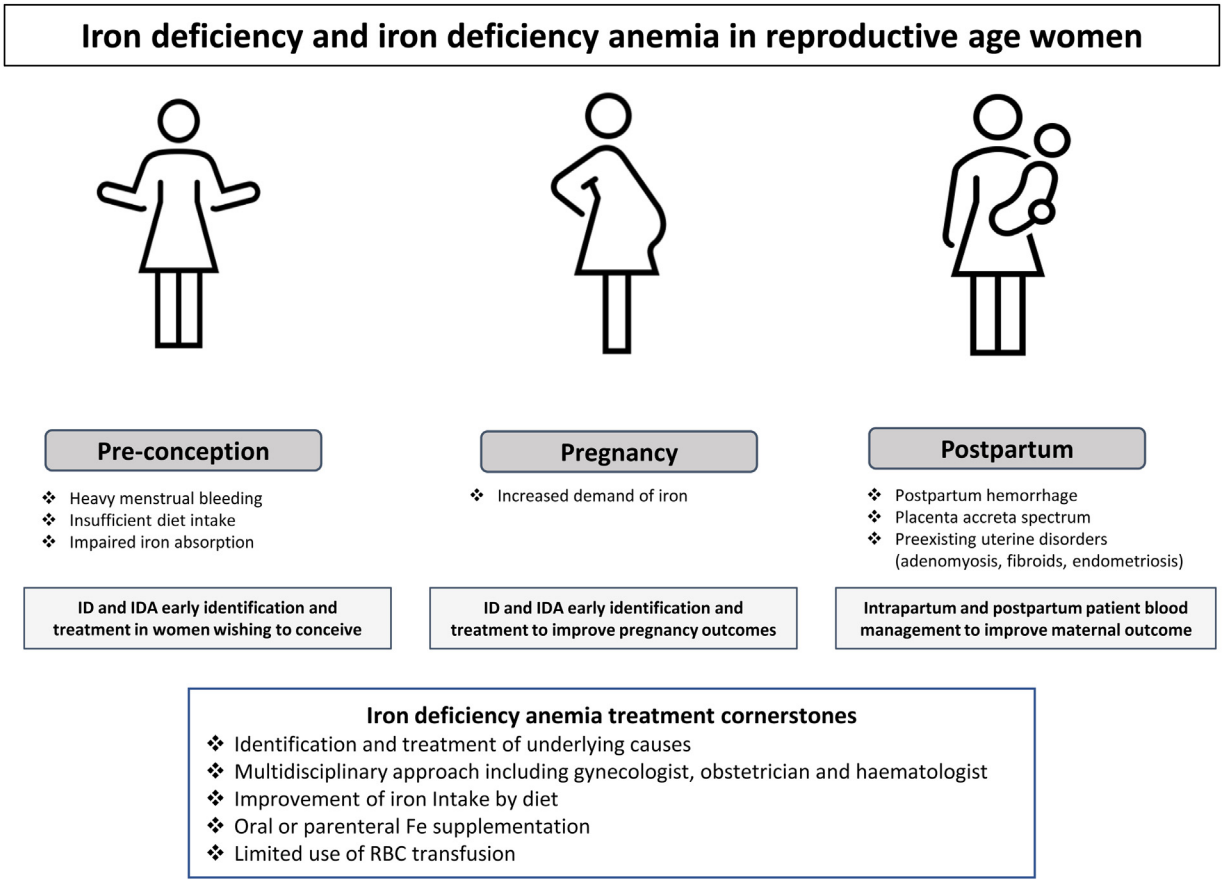

Fig. 1. Causes and cornerstores of management of iron deficiency and iron deficiency anemia in pre-conception, pregnancy and postpartum.

Table 1
Blood parameters in iron deficiency anemia (IDA) . *MCV, mean corpuscolar volume; TIBC, total iron binding capacity; UIBC, unsaturated iron binding capacity.*

- ↓hemoglobin (= anemia)
- ↓ Ferritin (<30 μg/L; in presence of inflammation <100 μg/L)
- MCV ↓ (microcytic) or normal (normocytic)
- ↓ Fe
- ↓ TSAT (normal range between 15% and 30%)

inflammatory state and may not correlate with ID. Thus, serum ferritin levels below 30 μg/dL indicate absolute ID when inflammation is absent, whereas in presence of inflammation, to indicate absolute ID serum ferritin levels are below 100 μg/L [69].

During the evaluation of the patient with IDA or ID, it is essential to perform a complete blood count including platelets, and basic coagulation screening tests – prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen. If a family history of bleeding disorder is also present and/or personal history of bleeding that is suspicious of an underlying bleeding disorder (as may be determined with screening questions to expose an underlying coagulopathy described with use of FIGO systems 1 and 2 [15]), then a referral of the patient to the hematologist is required.

An appropriate diagnosis and management of underlying causes of HMB [15], the leading to ID in reproductive age women, as well as managing ID/IDA during all stages of pregnancy is warranted. Implementing this approach could reduce the number of women living with disabilities, improving their QoL, and decreasing the large number (40%) of women entering pregnancy with ID/IDA.

This approach to patient care across the reproductive life course would improve pregnancy and infant outcomes, and thus avoiding unnecessary transfusions, the risk of preterm labor, low neonatal weight, perinatal complications, neonatal and maternal mortality, low tolerance to delivery blood loss, increasing infections, and reduced iron stores in newborns [2].

From AUB to IDA, a call to action before pregnancy

Menstruation is defined as repetitive uterine bleeding, regarded as a sign of reproductive health. When characterized by abnormal bleeding, it may reflect the presence of uterine diseases. Abnormal uterine bleeding (AUB) causes are classified by FIGO System 2, the PALM COEIN system [15–17]. Accordingly, the causes of AUB are classified into structural (Polyp, Adenomyosis, Leiomyoma, Malignancy, and Hyperplasia) and nonstructural (Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified) causes. Three key processes - vasoconstriction, hemostasis, and endometrial repair - are carefully coordinated to ensure appropriate menstrual blood loss (MBL) and concurrent endometrial repair and regeneration. Understanding the control of these processes during normal menstruation can help identify deviations that could lead to AUB/HMB and/or loss of function, ensuring successful implantation and/or maintenance of a pregnancy [18,19].

HMB is frequently under reported and many who menstruate normalize their monthly blood loss experience [3]. Although data from healthcare systems suggest a prevalence of 3%–5%, survey studies have shown us that the symptom of HMB may actually be present in as many as half the population of reproductive-aged women [19,20]. HMB is highly prevalent and adversely impacts quality of life (QoL). This may be attributable to inaccurate individual self-perception of HMB and normalization of symptoms [1,21].

AUB related to endometrial dysfunction (AUB-E) is a diagnosis of exclusion that indicates a fundamental problem in the processes required to control menstrual bleeding [19]. AUB is also common in women with uterine fibroids and adenomyosis likely a consequence of phenotypic endometrial changes [3,22]. For these patients with AUB, the medical history should encompass the evaluation of their menstrual cycle traits. This includes investigating the length of their cycle, the duration of their bleeding, the occurrence of clotting or heavy flow, and the frequency at which they need to change their menstrual products. Assessment of menstruation characteristics should refer to FIGO System 1 [15,16]. The effect of HMB on QoL should be assessed using specific tools, for example the Menstrual Bleeding Questionnaire [23–26]. An international collaboration of stakeholders (clinicians, patients, academics, guideline developers) from 20 countries and 6 continents has recently reported a core outcome set (COS) that includes variables that are feasible for use in clinical trials in all resource settings and apply to all known underlying causes of the symptom of HMB [27]. However, patient's self-reported QoL impairment across various domains should also be considered as clinically significant [27]. Furthermore, additional menstruation-related symptoms, including menstrual pain, dyspareunia, dyschezia, dysuria, and chronic pelvic pain, should be explored. Transvaginal ultrasonography (TVUS) is a fundamental tool to identify potential myometrial and endometrial causes of HMB. TVUS can systematically evaluate the myometrium and endometrium, identifying conditions such as uterine fibroids, adenomyosis, caesarean scar defects (CSD), and myometrial vascular abnormalities. A recent systematic review and meta-analysis has described the association between patients with CSD and AUB [28]. Such patients describe a unique bleeding pattern of prolonged menstruation and early-cycle intermenstrual bleeding. TVUS also provides an opportunity to assesses endometrial thickness, echogenicity, and possible presence of endometrial polyps or hyperplasia [3].

Menstruation and its disorders are unfortunately not sufficiently discussed due to a prevailing societal stigma and negative attitudes, even among healthcare providers. Many women lack awareness of the difference between normal and HMB. This "normalization" of HMB is usually established by parents and healthcare practitioners in adolescence and represents a barrier to care for affected girls and women [29].

IDA, a call to action during pregnancy

ID is common among pregnant women, as the developing fetus requires a relevant and increasing amount of the mother's iron reserves. By the first trimester, approximately 50% of non-anemic pregnant women exhibit ID, often stemming from pre-pregnancy conditions. Menstruation itself, with HMB, can significantly contribute to ID and IDA in preconception [30]. During pregnancy, iron requirements increase substantially, with pregnant women requiring 370 mg of iron for the fetus and placenta, and an additional 450 mg to enhance the erythrocyte mass in the third trimester [2].

An important factor contributing to anemia during pregnancy are the physiological changes that occur during gestation, regardless of any other causes of anemia that may be present. Plasma volume, red cell mass, and hemoglobin levels increase throughout pregnancy, but the rise in plasma volume is disproportionately greater than the increase in red cell mass or hemoglobin, resulting in "oligocythemic hypervolemia". In general, blood volume increases during pregnancy by 30–50 % from baseline levels. The hemodilution changes serve to reduce the viscosity of maternal blood and improve uteroplacental perfusion [31].

The American College of Obstetricians and Gynecologists (ACOG) guidelines released in 2021 address anemia in pregnancy but fall short in

recommending pre-conception ID and IDA screening [13]. The ACOG guideline highlights the significance of identifying ID and coordinating care with hematology. However, the guideline does not provide recommendations for screening ID and IDA in women who are planning to conceive. There is evidence that IDA is linked to an increased risk of low birth weight, preterm labor and birth, and peripartum complications such as placental abruption and postpartum hemorrhage, moreover anemic women are less able to tolerate peripartum hemorrhage [29].

Furthermore, the number of twin pregnancies is increasing in several countries, due to inappropriate assisted reproductive practices, higher than expected. A twin pregnancy, besides other risks, has high demands for iron, thus anaemia might be expected, and delivery complications prevented through early detection of anemia and iron supplementation.

In all pregnancies, the maternal and fetal risks are proportional to the severity of anemia starting in the second trimester. Furthermore, the impact of ID and IDA on pregnancy and fetal outcomes is more significant than commonly perceived. The potential impact of periconceptual ID and IDA on the developing fetus is particularly concerning due to evidence of potentially irreversible adverse effects on fetal neurologic development that have been linked to increased risks of various psychological and psychiatric outcomes [32,33]. It would be very timely to revisit the current paradigm that ignores iron status in reproductive-aged females outside of pregnancy. This is not only to reduce the need for oral or intravenous (IV) iron during and after pregnancy, but perhaps to ultimately improve fetal development, neonatal iron stores, and outcomes [32]. In 2023 the International Federation of Obstetrics and Gynecology (FIGO) issued an important statement on ID and anemia in women and girls [34]. The problem of ID/IDA is now being recognized in many countries, encouraging the release of national guidelines for the diagnosis and treatment of ID/IDA in women [35].

All these observations suggest that iron stores should be normalized in women planning to conceive, or rather in the interval between pregnancies. This approach may improve a spectrum of maternal and fetal outcomes while addressing the symptoms related to ID [29]. Moreover, prior to planning for pregnancy, it is recommended that all women have their hemoglobin and iron status (ferritin levels) checked. If ID is identified, it should ideally be corrected prior to trying to conceive [34] (Fig. 1).

IDA, a call to action for post-partum hemorrhage

Delivery, both spontaneous and operative, may be associated with unexpected blood loss. Postpartum hemorrhage (PPH) and consequent IDA are, unfortunately, still major complications occurring in pregnancy. Up to 25% of maternal deaths worldwide are due to PPH [36,37]. Whilst most women experiencing PPH have no known risk factors, those at risk could be identified quite easily if an accurate medical history is taken. Well known risk factors are previous PPH, placenta previa, abnormal placentation within the placenta accreta spectrum (PAS), multiple gestation and preeclampsia among others [38–40].

However, there are further risk factors for PPH and IDA of which obstetricians are be less aware. Reproductive specialists and gynecologists should point out to both women and obstetricians precisely these factors, including a history of infertility, particularly in combination with endometriosis as well as adenomyosis [41]. Women with a history of endometriosis, which incidentally often also entails a history of infertility treatment, have been shown to have a higher risk for placenta previa [42,43]. Furthermore, women with endometriosis and adenomyosis are at a greater risk for maternal and fetal complications [44,45]. The medical history of a pregnant patient should start with details about menstrual cycle characteristics and menstrual bleeding. The history of AUB, which includes HMB, in women of reproductive age, as defined by FIGO, can be a sign for a potential major risk if there is a PPH and the patient is anemic [16]. The IDA may be a consequence of pre-pregnancy HMB. Thus, PPH will be a greater risk if there is an underlying untreated IDA. Furthermore, a number of data show that women with IDA in pregnancy are at an increased risk for PPH and red blood cell transfusions [46].

Another important and still underestimated risk factor for PPH is abnormal placentation disorders, such as placenta accreta, increta or percreta. FIGO guidelines [47,48] report an increasing incidence over the last years and several ultrasound markers for PAS have been described [49,50]. However, the key message remains to check the location of placenta, ideally during the first trimester ultrasound to exclude PAS disorders, especially in case of previous uterine surgery [51,52] (Fig. 1).

Patient blood management and iron supplementation

Patient blood management (PBM) has been defined as “a patient-centered, systematic, evidence based approach to improve patient outcomes by managing and preserving patient's own blood while promoting patient safety and empowerment” [53].

PBM involves a multidisciplinary and multimodality strategy, which are captured with three main principles:

- Timely screening for and treatment of anemia and optimization of hemoglobin level
- Minimizing blood loss and optimization of hemostasis.
- Harnessing and optimization of the physiologic adaptation to anemia [2].

Especially in low-income countries, such as in the African continent, it is necessary to optimize the most common surgical procedure in order to reduce the blood loss, improving the QoL and reducing women’s morbidity and mortality.

Recently, the practice of PBM has become more common in obstetrics. PBM aims to optimize hemoglobin levels and hemopoiesis, to minimize peri-partum blood loss and to lower postpartum transfusion rates. PBM is based on three pillars:

1) Screening for and treating IDA.
2) Providing optimum peripartum management of PPH including cell salvage and autologous blood transfusion.
3) Restrictive transfusion practice after delivery [54,55]. Effectively applied, PBM has shown to reduce the need for peripartum red blood cell administration, which in itself is associated with certain risks [56,57] (Fig. 1).

Oral iron supplements are widely accessible, affordable, safe and effective. However, the downside is that more than 70% of people experience gastrointestinal side effects from oral iron. This often leads to poor compliance and, consequently, reduced effectiveness [58]. Recent findings show that serum hepcidin levels rise naturally and remain elevated for over 24 h following a single oral dose. This has led to the endorsement of alternate-day dosing, such that iron is absorbed more efficiently and this enhances the safety profile of oral supplementation [59,60].

Several chemical formulations of intravenous (IV) iron are also available, such as ferric derisomaltose, iron saccharate, ferric carboxymaltose (FCM) and ferumoxytol [68]. IV iron supplementation presents several benefits, including the swift recuperation of haemoglobin levels and iron reserves in the bone marrow. IV iron is a valid option for patients who cannot tolerate oral iron or do not respond to iron due to decreased absorption. In cases of severe anemia where haemoglobin levels are less than 7 or 8 g/dL and there is a need for quick recovery, IV iron is the preferred choice. This is particularly true during the 2nd and 3rd trimesters of pregnancy, where there is limited time for recovery and a high demand for rapid iron absorption [6], postpartum anaemia, and abnormal uterine bleeding [61]. A number of evidence regarding administration during pregnancy and postpartum pertains to FCM [63,64,65]. FCM maybe given directly into the vein up to 15-min infusion. The highest dose for direct, undiluted injection is determined by the patient’s weight, at 20 mg/kg, and should not go beyond this.

Additionally, each injection should not exceed 1,000 mg, and the total amount given should not surpass the patient's overall calculated need. Administration of FCM has been shown to be well tolerated, with rapid replenishment of iron stores [66,67] in pregnant women, and also in the postpartum.

Conclusion

ID and IDA exert a significant impact on QoL and women's health in their reproductive years. Educating patients on menstrual health and ensuring physicians' awareness of this issue are crucial for early management. A multidisciplinary team is imperative for addressing women's health throughout their reproductive journey. The diagnostic process begins with a thorough evaluation of familial and menstrual history, and especially exploring the presence of HMB. Treating the underlying causes of ID and IDA, along with iron supplementation, in the pre-conceptional period not only enhances women's health, but also improves pregnancy outcomes. Identifying risk factors for postpartum haemorrhage, screening for placenta accrete spectrum disorders, minimizing blood loss, and optimizing haemostasis constitute pivotal aspects of delivery management.

CRediT roles

- Felice Petraglia: Conceptualization; Writing - original draft, Supervision.
- Angela Gallone: Writing - original draft.
- Piotr Sieroszewski: Investigation, Data curation, Writing - review & editing.
- Drazen Pulanic: Investigation, Data curation, Writing - review & editing.
- Ingrid Marton: Investigation, Data curation, Writing - review & editing.
- Pavel Calda: Investigation, Data curation, Writing - review & editing.
- Lubomir Mikulasek: Investigation, Data curation, Writing - review & editing.
- Jarmila Zdanowicz: Investigation, Data curation, Writing - review & editing.
- Dragan Belci: Investigation, Data curation, Writing - review & editing.
- Silvia Vannuccini: Conceptualization; Investigation, Writing - original draft.
- Hilary Critchley: Conceptualization, Investigation, Data curation, Writing - review & editing.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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