the Management of Iron Deficiency and Iron-Deficiency Anemia in Women with Heavy Menstrual Bleeding

- Heavy menstrual bleeding (HMB) can be defined objectively as a total blood loss per menstrual cycle that regularly exceeds 80 mL.
- However, a definition requiring quantification of blood loss is only useful for research studies and accurate assessment of menstrual blood flow is difficult.
- Validated pictorial blood loss assessment charts have been developed, but these are recommended for use in research studies only and have limited value in clinical care.

- The UK-based National Institute for Health and Care Excellence (NICE) has therefore suggested that HMB should also be diagnosed when there is regularly excessive menstrual blood loss that ‘‘affects the physical, social, emotional or material quality of life of the patient’’.

- HMB is estimated to affect approximately 18–38% of women of reproductive age and may increase in prevalence for women approaching menopause.
- However, there is considerable variability in the reporting of HMB, and the condition is likely to be underdiagnosed.

- Heavy blood loss from menstruation can lead to depletion of iron stores, resulting in iron deficiency (ID).
- Prolonged blood loss, such as a menses duration of more than 7 days, or moderate blood loss in combination with an iron-deficient diet, such as often occurs in adolescents and vegans, can also contribute to the risk of depleted iron stores in women .

- Women with HMB lose on average five to six times more iron per menstrual cycle than women with a normal blood loss, resulting in totally depleted iron stores .
- Iron plays a key role in many physiological processes, including energy production, respiration, DNA synthesis and repair, myocyte function, and cell division .

- More than two-thirds of the body’s iron is bound as hemoglobin (Hb) within erythroid precursors and mature red blood cells (RBCs) .
- Severe ID can therefore lead to a fall in Hb levels, impairing RBC production, which in turn gives rise to normocytic or microcytic hypochromic anemia .

- The World Health Organization (WHO) defines anemia in nonpregnant women (age > 15 years) as a Hb concentration below 12.0 g/dL .
- ID is the most common cause of anemia and accounts for more than 60% of anemia cases worldwide, with preschool children and girls and women of reproductive age particularly affected .

- Some 30% of adolescents and women with HMB have been found to have ID (serum ferritin < 15 ng/mL) and 60% iron-deficiency anemia (IDA) .
- Mild-to-moderate IDA can be asymptomatic. When symptoms are present, they commonly include fatigue, weakness, and shortness of breath .

- Other symptoms may include headache, pica, hair loss, brittle nails, cold insensitivity, and restless leg syndrome .
- ID can lead to similar symptoms, and treatment of ID with iron therapy has been shown to improve physical activity and quality of life in patients predisposed to ID due to underlying chronic conditions, such as those with heart failure and inflammatory disease.

- IDA can significantly impair quality of life for women, and can lead to reduced cognitive ability and reduced productivity at work, as well as increased utilization of healthcare resources .
- Notably, isolated ID has also been shown to impair cognitive and physical performance in women, and exacerbate fatigue, with the impairments reversed by iron therapy .

- IDA prior to surgery is a risk factor for postsurgical morbidity and mortality, including increased risk of infections, major bleeding, average hospital length of stay, and perioperative blood transfusion in patients of all ages and geographic regions .
- Although less commonly investigated, preoperative ID irrespective of the presence of anemia has been shown to increase the incidence of postoperative mortality, serious adverse events, major cardiac and cerebrovascular events, and use of allogeneic blood transfusions; it also prolongs the length of hospital stay in patients undergoing cardiac surgery .

- Studies have shown that treatment of ID/IDA prior to surgery can reduce the required number of post-treatment blood transfusions while simultaneously improving hematological parameters .
- Anemia poses particular challenges when women undergo surgery, particularly for the treatment of their HMB:
- around 23% of women scheduled for an elective hysterectomy or myomectomy have anemia .

- Data from an analysis of more than 12,000 women undergoing gynecological surgery in the USA showed that operative morbidity and mortality were increased in those with anemia .
- Notably, the risks associated with preoperative anemia were not eliminated by perioperative transfusions .

- Evidence suggests that the diagnosis and effective treatment of ID/IDA in patients with HMB improves health outcomes and quality of life.
- Iron therapy in menstruating women with ID has been shown to reduce fatigue levels, while in patients with ID or IDA, intravenous (IV) iron treatment prior to hysterectomy reduced the prevalence of postoperative anemia and utilization of postoperative blood transfusion compared with no iron treatment .

Screening for Anemia

- Most guidelines included guidance on screening women with HMB for anemia .
- However, the guidance varied with respect to the universal use of screening versus criteria-led testing, identifying relevant symptoms, and diagnostic Hb level.

- most guidelines recommended routine initial assessment of Hb levels or a full blood count for all women presenting with HMB .
- Two further guidelines recommended routine assessment of Hb or a full blood count for women with HMB who also met specific criteria—namely an appropriate medical history and/or bleeding score ,or the presence of physical or psychological symptoms indicative of ID/IDA .

- quantification of Hb or a full blood count, specified a threshold Hb level indicative of anemia (< 12 g/ dL and <10 g/dL , respectively).
- evaluating symptoms of ID/IDA/anemia during the initial assessment, the specific signs and symptoms of anemia or ID/IDA to check for in the patient .
- pallor , shortness of breath with or without activity , and lightheadedness/dizziness were the most commonly stated signs and symptoms.

Screening for ID

- measurement of iron levels in women with HMB
- advised the use of serum ferritin as an indicator of iron status
- iron therapy for IDA can be initiated on the basis of Hb levels from a full blood count, without the need for ferritin measurement.
- assessment of iron levels as part of second-line or supplementary investigations in cases where anemia had been confirmed or in non-anemic patients with overt symptoms of ID.

- testing all patients with confirmed anemia for the presence of ID while another recommended testing for ID when anemia did not respond to oral iron therapy.
- tests for serum iron in an additional battery of tests to be considered, but did not specify criteria for conducting them.
- specific serum ferritin thresholds for diagnosis of ID/IDA, with both<15 lg/L and< 30 lg/L given as levels consistent with ID.

- Ferritin is an intracellular glycoprotein that binds iron, and low serum ferritin levels indicate diminished iron stores and thus ID.
- Serum ferritin tests are easily available, inexpensive to conduct, and an accurate measure of iron levels in women of reproductive age with no concomitant disease.
- However, as noted in one of the guidelines ,while low ferritin always indicates low iron stores, serum ferritin may be normal in patients with inflammatory disorders; thus a normal serum ferritin result does not fully rule out ID.

- total ironbinding capacity (TIBC), hypochromic blood film, and serum soluble transferrin receptor (sTfR) if ferritin levels are normal , or transferrin saturation (TSAT) if ferritin levels are elevated.

- use of TSAT if Hb levels are < 12 g/dL, or to assess erythrocyte morphology and consider a microcytic hypochromic phenotype to be indicative of IDA.
- RBCs with a low mean corpuscular volume (microcytosis) or mean corpuscular Hb concentration (hypochromic) may be indicative of ID, and these guidelines recommend testing serum ferritin levels in women suspected of having ID.

Management of Iron Deficiency

- guidelines recommended treating patients with ID irrespective of the presence or absence of anemia ,with two also recommending prophylactic oral iron therapy for patients who are asymptomatic but at high risk of developing ID or IDA .
- Two of the guidelines specifically recommended continuing iron treatment until iron stores are replete .

Management of Anemia/IDA: Iron Therapy

- guidelines recommended oral iron administration as the preferred route of treatment if permitted by the patient’s health and circumstances, not only for patients with confirmed ID/IDA but also for those at high risk of developing ID/IDA .

- If there is sufficient time prior to surgery, oral iron administration can be used to normalize a patient’s Hb .
- However, both the American College of Obstetricians and Gynecologists and Health Quality Ontario specified that oral iron therapy is only appropriate in cases of nonsevere anemia .

- Similarly, only five guidelines provide recommendations on the use of IV iron therapy in preference to oral iron therapy, and this was advised as a first-line strategy under certain circumstances—including clinical scenarios warranting immediate correction of anemia, such as imminent surgery ,or following gastrointestinal or bariatric surgery .

- IV iron treatment was also recommended for patients with severe anemia and a Hb level < 9 g/dL .Guidelines also recommended IV iron therapy as a second-line treatment in patients with poor compliance and/or intolerance to oral iron therapy ,as well as in those who did not respond to oral iron therapy .

- There was a notable lack of guidance around how to select patients for oral versus IV iron therapies, with only Health Quality Ontario recommending a specific threshold of 9 g/dL for use of IV iron administration .
- In several instances, guidelines did not specify whether iron should be given orally or IV in women diagnosed with ID/IDA .

Non-Iron-Based Correction of ID/IDA

- recommended blood transfusion for severe anemia, and all recommended basing the treatment decision on the severity of anemia and/or patient symptoms .
- Specifically, one guideline stated that transfusion should only be used in cases of acute hemorrhage or hemodynamic instability; one recommended basing the decision to transfuse on the severity of symptoms (with transfusion recommended in patients with hypotension, chest pain, syncope or tachycardia ,and two recommended that Hb levels should be examined in addition to symptoms .

- The recommended Hb threshold varied, with one guideline advising consideration of transfusion as a first approach to treatment if Hb levels are <6 g/dL in symptomatic patients or <5 g/dL in those who are asymptomatic , while a second guideline noted that otherwise healthy adolescents may tolerate Hb levels < 7 g/dL, and stated that the decision to transfuse should not be based solely on Hb levels but should also consider hemodynamic status .

- Iron intake may also be boosted through dietary interventions such as increasing consumption of foods rich in heme iron (clams, oysters, shrimp, sardines, liver, red meat), and reducing consumption of foodstuffs that can block iron absorption, including tea and coffee .
- However, dietary intervention was only recommended in conjunction with iron therapy .

TREATMENTS TO REDUCE BLOOD LOSS FROM HMB

- Several guidelines included recommendations for medical treatments to reduce blood loss from HMB by addressing the underlying cause .
- Hormonal treatments were commonly recommended .
- The 52 mg levonorgestrel-releasing intrauterine system (LNGIUS) was the most consistently recommended hormonal treatment approach ,with the UK-based NICE recommending to consider an LNG-IUS as first-line treatment for women with HMB but no identified pathology, uterine fibroids > 3 cm in diameter, or suspected or diagnosed adenomyosis .

- Other progestogen-only methods, such as depot medroxyprogesterone acetate, and combined oral contraceptive pills (estrogens plus progestogen), can also markedly reduce HMB ,including in adolescents .
- Gonadotropin-releasing hormone (GnRH) analogues may be used as a short-term solution to boost iron stores in women due to undergo surgery or in those who are experiencing HMB as a result of uterine fibroids .

- One set of guidelines also recommended considering the use of GnRH analogues to reduce HMB in women in whom other medical or surgical treatment options had failed or were contraindicated .
- Selective progesterone receptor modulators (SPRM) may also be used in the short term to correct anemia in patients with fibroids .
- However, ulipristal, the only licensed SPRM in the USA and the European Union, had its European license withdrawn in March 2020 because of safety issues .

- Non-hormonal treatments are recommended for reducing blood loss from HMB in patients in whom hormonal treatment is not appropriate or desirable, as a second-line option after hormonal treatment, or as first-line treatment in patients with abnormal uterine function or fibroids .
- The most frequently recommended options were non-steroidal antiinflammatory drugs (NSAIDs) and antifibrinolytic agents such as tranexamic acid .
- Non-hormonal treatments were considered particularly effective in controlling HMB for women with more predictable periods and in those who are planning a pregnancy.

- Consequently, most guidelines recommending only full blood counts will miss diagnosis of ID.
- While the limitations of measuring serum ferritin as a proxy for iron levels were cited in several guidelines, there was no consensus on an optimal alternative (potential candidates include TIBC, serum sTfR, and TSAT).
- In the recently released WHO guidelines, ferritin concentration is strongly recommended as a good marker to diagnose iron deficiency in otherwise healthy individuals.

- The WHO also specifies a cutoff threshold of <15 lg/L, which is cited by the American College of Obstetricians and Gynecologists guidelines on HMB management and concurs with the recommendations by Health Quality Ontario.
- Conversely, this is lower than the <30 lg/L threshold given by the Saudi Arabian and US expert panel guidelines .

- This higher threshold is supported by the evidence that ferritin <30 lg/L has a 98% sensitivity and 92% specificity for detecting ID in patients with anemia .
- As well as the uncertainty surrounding the most accurate parameter to measure, the paucity of recommendations to test for iron levels in women with HMB may reflect a lack of understanding regarding the benefits of treating ID in the absence of anemia.

- This is somewhat surprising, given that iron therapy has been shown in multiple settings to be effective in women with HMB .
- This may be because the guidelines are often targeted at specialists treating HMB, covering the diagnosis of ID/IDA as part of the HMB workup on the assumption that patients will then be referred to the family practitioner for treatment of any diagnosed ID/IDA.

- For this reason, there are often separate guidelines available on the management of ID/IDA that are not targeted to a specialty or patient group.
- Among the eight guidelines providing some recommendation, further guidance is required on when IV iron therapy is appropriate and what Hb thresholds should be used to choose between the use of oral and IV iron therapies.

- Generally, when ID or IDA is confirmed, oral iron administration is recommended in HMB guidelines as first-line treatment, with IV iron administration advised in patients who cannot tolerate or do not respond to oral iron therapy.

- However, it is common for oral iron therapy to be poorly tolerated because of gastrointestinal side effects, which often results in poor adherence .
- It is also notable that oral iron therapy has a limited capacity to restore iron levels when there is moderate to severe anemia, in which case IV iron therapy is required to achieve rapid and complete restoration of Hb levels .

- Several guidelines recommend the preferred use of IV iron therapy when patients require rapid elevation of Hb levels, but this is restricted to particular criteria, such as prior to imminent surgery .
- Notably, dietary intervention was recommended by three guidelines and only in conjunction with iron therapy.

- Importantly, in recommending correction of ID/IDA prior to surgery, these guidelines align with the first pillar of patient blood management (PBM) recommended in the wider surgical setting, which advocates treatment of preoperative anemia and optimization of RBC mass prior to surgery .

- PBM is increasingly being adopted as a way to improve patient outcomes and reduce transfusion requirements and costs .
- The use of PBM to reduce the global usage of blood transfusions becomes increasingly important when global blood supplies are restricted—for example during pandemics such as the recent COVID-19 pandemic, which halted blood collections and reduced the eligible donor population.

- PBM has demonstrated success as a strategy to reduce transfusions in anemic women undergoing gynecological surgery .
- In a study of eight women with HMB undergoing gynecological surgery who refused blood transfusions, severe anemia (Hb <5 g/dL) either pre- or postoperatively could be effectively managed with IV iron therapy and erythropoiesis-stimulating agents alone.

- As part of pillar 1 of PBM, it is recommended to screen for anemia once patients are scheduled for surgery, inform patients about the risks of preoperative anemia and benefits of treatment, and treat ID/IDA and replenish iron stores before surgery .

- About half of the included guidelines provided advice on pharmacological therapies to minimize or reduce blood loss from HMB.
- The 52 mg LNG-IUS was the most frequently recommended medical intervention; otherwise, there was generally a lack of consensus across guidelines with regard to recommendations for pharmacological interventions.

- Where pharmacological intervention is recommended to reduce blood loss, guidance on iron supplementation to restore iron levels is often missing.
- For example, it can take over a year for serum ferritin levels to normalize in patients with HMB treated with an LNG-IUS, yet quality of life could be improved more quickly with immediate iron supplementation .

- ID and IDA are likely to be underdiagnosed and undertreated in patients with HMB.
- One of the challenges to managing women with HMB is the involvement of multiple healthcare practitioners without clear guidance for those ultimately responsible for identifying and treating the resultant ID/IDA.
- There needs to be a consensus HMB guidance to cover all aspects of care, to improve health outcomes in these patients.

THANK YOU