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Dr. Christine Lett, is an assistant professor at the University of Saskatchewan. She is an Obstetrician/Gynecologist in community practice in Regina, Saskatchewan, where she is also the department head. She has a passion for quality improvement. When she started learning about iron deficiency, she recognized that a significant number of her patients were iron deficient and had the opportunity for better care.

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The Treatment of Heavy Menstrual Bleeding in 2024

Christine Lett, MD, FRCSC

Introduction

Heavy menstrual bleeding and iron deficiency are both commonly underrecognized and undertreated conditions.[1] In fact, over 2 billion people globally are iron deficient.[2] Iron deficiency disproportionately impacts reproductive-aged women and negatively impacts their quality of life.[2] The most common etiology of iron deficiency anemia in premenopausal women is excessive menstruation.[3] Heavy menstrual bleeding is defined as excessive menstrual blood loss, which interferes with a woman's quality of life.[4] Heavy menstrual bleeding is one of the most common reasons for gynecologic consultation,[4] and impacts one-third of reproductive-aged women. Improving the quality of life for women with heavy menstrual bleeding requires recognizing the condition, identifying its cause, ruling out iron deficiency, and tailoring treatment to reduce menstrual blood loss and replenish iron stores.

Diagnosis and Classification

The diagnosis of heavy menstrual bleeding can be obtained by the patient's history alone. Intermenstrual and postcoital bleeding require investigation to rule out underlying pathology. Postmenopausal bleeding is concerning for underlying malignancy and must be investigated. This article addresses premenopausal bleeding only.

Identifying the etiology of heavy menstrual bleeding is important because the cause of the bleeding will determine how best to stop it. The PALM-COEIN classification system is useful for describing the causes of heavy menstrual bleeding.[5] **Table 1** summarizes the PALM-COEIN classification system with suggested investigations and treatments for each cause of heavy menstrual bleeding.

Investigations

Rule out pregnancy

If pregnancy cannot be excluded by the patient's history, a urine or serum beta-human chorionic gonadotropin (BHCG) test is appropriate.

Rule out iron deficiency and anemia

A complete blood count (CBC) and ferritin test should be completed on all patients with heavy menstrual bleeding[6] because of the high prevalence of iron deficiency among reproductive-age women.

	Key Investigations	Treatment Options
Polyp	CBC, iron studies, ultrasound	TXA, iron for ID, polypectomy
Adenomyosis	CBC, iron studies, ultrasound	TXA, iron for ID, hormones, hysterectomy
Leiomyoma	CBC, iron studies, ultrasound	TXA, iron for ID, hormones, myomectomy or hysterectomy
Malignancy and hyperplasia	CBC, iron studies, endometrial biopsy	TXA, iron for ID, hormones, hysterectomy
Coagulopathy	CBC, iron studies, history, special lab tests	TXA, iron for ID, correct coagulopathy, surgery
Ovulatory Dysfunction	CBC, iron studies, history	TXA, iron for ID, hormones
Endometrial	CBC, iron studies, ± endometrial biopsy	TXA, iron for ID, hormones, surgery
Iatrogenic	CBC, iron studies, ultrasound, ± endometrial biopsy	TXA, iron for ID, change hormone therapy, surgery
Not otherwise specified	Etiology not yet understood	TXA, iron for ID

Table 1. Suggested investigations and treatment options by PALM-COEIN classification; *courtesy of Christine Lett, MD, FRCSC.*

Abbreviations: CBC: complete blood count, **TXA:** tranexamic acid, **ID:** iron deficiency, **Hormones:** hormonal suppression of menses

The World Health Organization defines anemia in women as a hemoglobin level <120 g/L.[7] However, this definition of anemia is based on a population sample that includes iron deficient women and is therefore not an ideal value. The target hemoglobin level for optimal health is 140 g/L.[3] Preoperatively, the target hemoglobin level should be ≥130 g/L.[8] Iron deficiency is diagnosed when the ferritin level is <30 ng/mL or the transferrin saturation (TSAT) is <20%.[8] In patients who do not eat meat, adding a vitamin B12 test is appropriate.

Rule out malignancy

Ruling out endometrial hyperplasia and cancer is key for women at risk. Endometrial sampling is indicated for women with the following risks for endometrial cancer: body mass index (BMI) over 30 kg/m^2, nulliparity, diabetes, polycystic ovary syndrome, hereditary cancer syndromes, significant intermenstrual bleeding, failure of medical management, and prolonged periods of amenorrhea.[9] An office endometrial biopsy is the most expeditious way to obtain a tissue diagnosis. While age is also cited as a risk factor for endometrial hyperplasia and cancer, with guidelines recommending endometrial sampling in women over age 40[9] or age 45,[5,10] a Canadian review of endometrial biopsies on women aged 41–49 without other risk factors for endometrial cancer showed no malignancies on biopsy.[11]

Ruling out underlying gastrointestinal (GI) malignancy should also be considered. Bidirectional endoscopy is recommended for asymptomatic premenopausal women with iron deficiency anemia.[12]

Ultrasound

Imaging the uterus is required to rule out structural causes of heavy menstrual bleeding, such as polyps, fibroids, and adenomyosis. Ultrasound is typically the most easily accessible imaging modality. In select cases, hysteroscopy or magnetic resonance imaging (MRI) are required.

Other investigations

The patient's menstrual history may prompt further blood work. For example, when ovulatory dysfunction is suspected by the patient's history, levels of thyroid stimulating hormone (TSH), prolactin, and an androgen panel may be appropriate. If a patient has had heavy menses since menarche or has a family history of a bleeding disorder, a bleeding disorder work-up should be ordered.[13]

The source of iron deficiency is often heavy menstrual bleeding, but there may be another underlying cause for iron deficiency. Ruling out poor nutritional intake, malabsorptive conditions, Celiac disease, and GI malignancy should not be neglected.

Treatment

Medical management is the first line of treatment for managing heavy menstrual bleeding.[9] Many of the medical options listed in **Table 1** are used off-label and they are very effective. Treatment must be tailored to the patient's goals. For example, many hormonal options will prevent pregnancy. My preferred approach for most patients is tranexamic acid (TXA) 1000–1500 mg orally 3 times a day for 5 days with heavy menses because this works immediately with their next menses. I add a levonorgestrel intrauterine system (LNG IUS) if pregnancy is not desired. Recognizing and replacing iron deficiency will further improve her quality of life. Anemia should be corrected before proceeding with surgical management.

Tranexamic acid

TXA is an antifibrinolytic medication that reduces menstrual blood loss by 40% to 59% from baseline.[9] TXA can safely be prescribed for most women because absolute contraindications are rare.[14] Some women find TXA adequate for symptom control. For those who choose other medical or surgical management options, I recommend using TXA with menses until the chosen treatment option is effective. All other medical treatment options often take at least 1–3 months to improve menstrual blood loss, and surgical wait times can be even longer.

TXA has been extensively studied in diverse patient populations. There is controversy about the risk of venous thromboembolism (VTE) with TXA treatment. There is no increased risk of VTE when TXA is used in postpartum hemorrhage or when it is given within 3 hours of trauma.[15] However, an increased risk of VTE was observed with TXA use in acute GI bleeds.[16] One population study of women who filled a prescription for TXA demonstrated a very small increased risk of VTE, with a number needed to harm per 5 days of treatment of 1 in 78,549.[17] It is postulated that heavy menstrual bleeding itself is a risk factor for VTE.[9,18] In addition, a recent study demonstrates that iron deficiency anemia is a risk factor for VTE.[19] My interpretation is that women with heavy menstrual bleeding are at risk for VTE because of iron deficiency anemia, and therefore, reducing the bleeding with TXA is key to preventing further iron loss and the associated risk of thrombosis from iron deficiency.

There is a theoretical concern that the use of TXA with combined hormonal contraceptives (CHC) increases the risk of VTE because of one case report of coronary artery thrombosis with the combination of these medications.[20] The absolute risk of VTE in CHC users is 9–10/10,000 woman years, double the baseline risk of 1–5/10,000 woman years among non-CHC users, while the risk of VTE with the combination of CHC and TXA is unknown.[21] Among postpartum women, who have a 300/10,000 woman year risk of VTE,[21] given TXA in the setting of postpartum hemorrhage, there was reassuringly no increased risk of VTE.[22] Based on this data, I confidently use TXA and CHC concomitantly.

Hormonal suppression

Hormonal suppression of menses has been well described elsewhere[9]; therefore, a detailed discussion is beyond the scope of this review. The 2 mechanisms of action, hormonal-induced thinning of the endometrium, and suppression of ovulation, both result in reducing menstrual blood loss. Because the LNG IUS has the advantage of

fewer systemic adverse effects than other options for hormonal suppression of menses, along with an up to 85% reduction in menstrual blood loss, I offer this option as a first line treatment to most patients. The National Institute for Health and Care Excellence (NICE) recommends the LNG IUS as a first line treatment option for women without identified pathology, with fibroids less than 3 cm in diameter, and for those with adenomyosis.[4]

When regular cyclic bleeding is desired, combined hormonal contraception (CHC) is prescribed in a cyclic regimen. I typically start with a monophasic pill containing 30 mcg of ethinyl estradiol. Once cycle control is acceptable with cyclic use, an extended cycle regimen can be trialled. My experience is that bothersome breakthrough bleeding is more common with low-dose CHC or when an extended cycle regimen is initiated.

Fibroids are a common cause of heavy menstrual bleeding and can be managed with all forms of hormonal suppression of menses. Three classes of hormonal treatment for fibroid-associated heavy menstrual bleeding deserve mention. Ulipristal acetate, a selective progesterone receptor modulator, is no longer available due to reports of liver failure. When surgery is planned for fibroids, pretreatment with a gonadotropin-releasing hormone (GnRH) agonist, leuprolide acetate, should be considered.[23] A new class of medication, GnRH receptor antagonists, work by competitively binding to pituitary GnRH receptors, blocking endogenous GnRH signalling, which leads to reversible, dose-dependent, decreases in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations. Relugolix CT, a GnRH antagonist, includes 1 mg of estradiol and 0.5 mg of norethindrone acetate as add-back therapy. The purpose of this add-back therapy is to mitigate the adverse effects of hypothalamic hypogonadism.

Surgery

In general, surgery is reserved for patients who experience a failure of medical management. First line treatment with surgery may be required in some cases. For example, symptomatic endometrial polyps and submucous fibroids often require hysteroscopic surgery for symptom control. Hysterectomy provides definitive management for heavy menstrual bleeding. Opportunistic salpingectomy should be offered at the time of hysterectomy, and hysterectomy should be performed vaginally or laparoscopically whenever technically feasible.[23] Oophorectomy should not be done in premenopausal women in the absence of malignancy.[23]

Multiple national and international guidelines strongly recommend that anemia be corrected before surgery.[8,23-25] Anemic patients have a significantly increased risk of adverse perioperative outcomes, including surgical site infection, VTE, major bleeding, and end-organ dysfunction such as cardiovascular, respiratory, and renal dysfunction. Patients with preoperative anemia also have an increased risk of perioperative death. Anemia should be identified and corrected before surgery is performed.

Iron supplementation

Oral iron salts are the first line treatment for the management of iron deficiency and anemia.[26] There are 3 iron salts used in supplements: ferrous gluconate, ferrous sulphate, and ferrous fumarate, which all can be dispensed as 300 mg tablets. Each formulation contains a different amount of elemental iron, with ferrous fumarate containing the most elemental iron (100 mg per tablet). Oral iron should be taken daily, or every other day, on an empty stomach. Vitamin C supplementation does not enhance iron absorption in healthy individuals.[27] A repeat hemoglobin level should be ordered 4 weeks after initiating oral iron therapy. An appropriate response to oral iron supplementation is demonstrated when the hemoglobin level increases by 20 g/L over a period of 4 weeks for anemic patients. Oral iron supplementation is required for at least 3 months after achieving a normal hemoglobin level to replenish iron stores.

Intravenous iron provides a rapid replenishment of iron stores. Four formulations are available in Canada. Sodium ferric gluconate complex in sucrose injection (Ferrlecit®) is used in dialysis patients. Iron sucrose (Venofer®) has been available and used for decades, but its use is off-label outside the context of chronic renal disease. The maximum one-time dosing of iron sucrose in my centre is 300 mg, per infusion, administered over 90 minutes. Newer iron formulations safely provide larger doses of iron at once over a shorter infusion period. Ferric derisomaltose (Monoferric®) is approved to treat iron deficiency anemia in adults and is dosed at 1000 mg or 1500 mg per infusion, administered over 20–30 minutes (Monoferric monograph).[28] Ferric carboxymaltose (Ferinject®) is approved to treat iron deficiency anemia in pediatric and adult

patients and is expected to be on the Canadian market by the end of 2024. A maximum adult dose is 1000 mg per infusion, administered over 15 minutes. Ferric carboxymaltose is associated with transient hypophosphatemia in 45% of patients, which can be managed expectantly for most patients.[29]

The indications for intravenous iron in anemic women include:[8,26]

1. Oral iron supplementation is not tolerated, typically due to GI side effects
2. Lack of response to oral iron supplementation, <20 g/L hemoglobin level increase over a period of 4 weeks
3. Profound anemia (hemoglobin level <80 g/L)
4. Anemia and surgery planned within 8 weeks

Accessing intravenous iron differs between institutions. Becoming familiar with arranging intravenous iron in your area will expedite your patient's care.

Conclusion

Heavy menstrual bleeding and iron deficiency are very common conditions, but neither condition is normal, and both negatively impact a woman's quality of life. In reproductive-aged women, iron deficiency is frequently due to menstrual blood loss. The first line of management for heavy menstrual bleeding is medical treatment. A two-pronged approach is required to successfully manage iron deficiency in heavy menstrual bleeding, stop the excess bleeding, and replace iron stores.

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Financial Disclosures

None declared.

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