BEST PRACTICES IN: The Treatment of Heavy Menstrual Bleeding

Introduction

Heavy Menstrual Bleeding (HMB) is a common gynecologic complaint, affecting millions of women.[1] Although HMB resulting in serious anemia or other complications of volume depletion is relatively uncommon, the heavy periods may significantly impair physical and social activities affecting quality of life. Heavy Menstrual Bleeding is also associated with depression, insomnia, fatigue, and other forms of psychological distress in patients, but the impact of treatment on these conditions has not been clinically demonstrated.[2-5] The financial impact of reduced productivity related to HMB is estimated at approximately $1,700 per woman per year.[3]

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There are two main treatment approaches to HMB: surgical and pharmacologic. Surgical interventions include endometrial ablation techniques and hysterectomy. Although both are effective (the latter being considered curative), they carry the expenses and risks typically associated with surgery and are obviously inappropriate for women who may want to maintain their ability to become pregnant.

Several pharmacologic therapies that reduce heavy menstrual bleeding to various degrees are in use, including both hormonal and nonhormonal options. Oral contraceptives are used "off-label" to reduce heavy menstrual bleeding, and a levonorgestrel-releasing intrauterine system is approved by the US Food and Drug Administration (FDA) for the treatment of HMB in women desiring contraception with this method. Both of these hormonal strategies are considered effective but are inappropriate for women who do not want or cannot tolerate hormones. The oral formulation of tranexamic acid (Lysteda®) received FDA approval for the treatment of HMB, thus providing physicians with a nonhormonal treatment option proven effective for the management of HMB.

Definition & Diagnosis

HMB is quantitatively defined as total blood loss exceeding 80 mL per cycle or menses lasting longer than 7 days.[6] However, in practice, HMB is defined as "excessive menstrual blood loss [that] interferes with a woman's physical, social, emotional, and/or material quality of life."[6] There are no formalized screening or diagnostic procedures for HMB. Women may be asymptomatic and unaware of menstrual irregularities or present with fatigue, shortness of breath, or other symptoms typical of excessive blood loss. Therefore, the diagnosis of HMB is based on a combination of patient history, perception of menstruation, physical examination, and the severity of related psychosocial sequelae.

The underlying causes of HMB may be organic, endocrinologic, anatomic, or iatrogenic (**Table**).[6] When a woman's history suggests HMB without any structural or histological abnormalities, medical treatment can be started without any additional investigations.[7] In other circumstances, additional studies including ultrasound and biopsy may be warranted.[7]

Table. Causes

Organic	Anatomic
• Infection	• Uterine fibroids
• Bleeding disorders	• Endometrial polyps
• Organ dysfunction	• Endometrial hyperplasia
	• Pregnancy
Endocrinologic	**Iatrogenic**
• Thyroid and adrenal gland dysfunction	• Intrauterine devices
• Pituitary tumors	• Steroid hormones
• Anovulatory cycles	• Chemotherapy agents
• Polycystic ovary syndrome	• Medications (eg, anticoagulants)
• Obesity	
• Vasculature imbalance	

Source: Shaw JA[6]

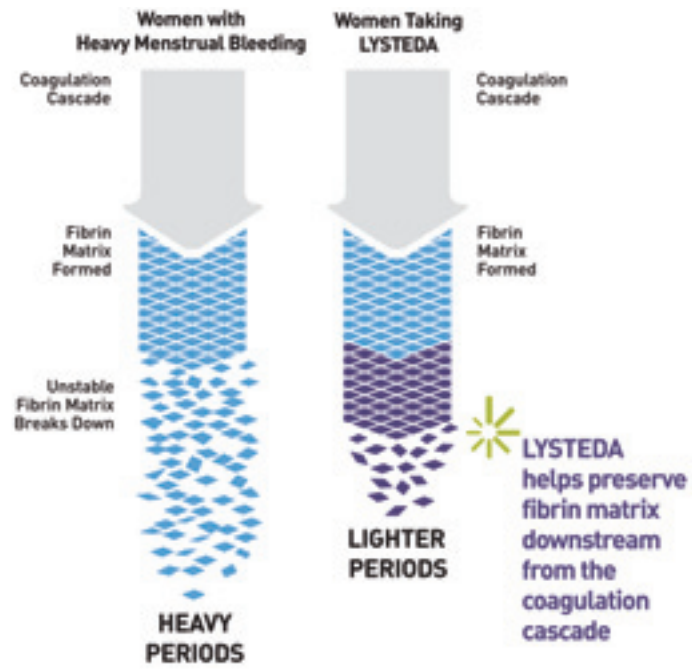
Tranexamic Acid for the Treatment of HMB

Outside of the United States, tranexamic acid has been used for decades for the treatment of heavy periods, but it has only recently received FDA approval for the treatment of Heavy Menstrual Bleeding. Tranexamic acid is unique among available treatment options for HMB because it is nonsurgical, nonhormonal, and specifically indicated to treat HMB. Most women who experience heavy bleeding with their menstrual period have normal coagulation. Blood clots form in the coagulation cascade and then fibrin—the mesh-like fibers that bind a blood clot together—is deposited in the clot. In the normal fibrinolytic process, tissue plasminogen activator catalyzes the conversion of plasminogen to plasmin, the active enzyme. Plasmin, in turn, dissolves fibrin. Women who have HMB dissolve the fibrin at an accelerated rate, causing heavy periods. Tranexamic acid reduces cyclic HMB by acting downstream of the coagulation cascade to slow the dissolution of fibrin and maintain the integrity of the clot, thereby reducing menstrual bleeding (**Figure**).

In a double-blind phase III trial, 196 women with quantitatively defined HMB (mean blood loss >80 mL per cycle) were randomized to receive tranexamic acid 3.9 g/day or placebo for up to 5 days per menstrual cycle for six cycles.[8] The final intent-to-treat population included 187 women, 72 randomized to placebo and 115 to tranexamic acid. The primary efficacy end point was the mean reduction in menstrual blood loss from baseline meeting three criteria: (1) a significantly greater reduction than placebo, (2) a reduction >50 mL, and (3) a reduction greater than a predetermined meaningful threshold (≥36 mL). The trial also measured health-related quality of life using a validated patient-reported outcome instrument.

All women treated with tranexamic acid met the primary efficacy end point. There was a 38% reduction in mean menstrual blood loss with tranexamic acid versus 12% with placebo ($P<0.001$), and the reduction in blood loss from baseline was >60 mL with tranexamic acid, which exceeded the predetermined meaningful threshold of 36 mL. All women treated with tranexamic acid had significant improvements in quality of life ($P<0.01$),[8] defined as reductions in limitations to social and physical activities. Adverse events with tranexamic acid were considered typical of menstruation, including headache, sinus and nasal symptoms, back pain, abdominal pain, joint pain, and menstrual discomfort/cramps, and were generally similar to placebo. No thromboembolic events were observed in the clinical studies.[8] Nevertheless, because of its antifibrinolytic effect, tranexamic acid is contraindicated in woman with an increased risk of thromboembolism and should be used concomitantly with oral contraceptives only if absolutely necessary.[9]

Figure. Mechanism of Action of Tranexamic Acid



*Artistic interpretation of the mechanism of action. This is not a visual representation of the significant efficacy seen with LYSTEDA. In the 6-cycle pivotal trial, LYSTEDA reduced monthly periods by 66 mL on average, a 38% overall reduction (vs 18 mL [12%] for placebo).

Source: Ferring Pharmaceuticals

Conclusions

Tranexamic acid is well tolerated, convenient, and effective and does not alter fertility. It may be prescribed to any woman with confirmed HMB not requiring hormonal contraception provided there is no underlying pathology requiring treatment (eg, cancer, endometrial hyperplasia). Tranexamic acid's onset of action may occur rapidly—there is no acclimation period—efficacy may be observed as early as the first period. FDA approval of Lysteda confirms the efficacy and tolerability of the agent and provides physicians with a reliable option for the management of HMB.

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