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COMMENTARY

Antiplatelet period drama: a rush of blood or classic crimson tide?

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At least 25% to 30% of menstruating individuals are affected by heavy menstrual bleeding (HMB), though this likely represents a gross underestimation given the lack of recognition and underdiagnosis [1,2]. HMB is associated with significant impairments in both health and quality of life and remains a major contributor to iron deficiency with or without anemia among individuals of reproductive age [3]. Among those receiving anticoagulants, the prevalence of HMB is considerably higher, accounting for approximating 60% to 70% of menstruating individuals [4]. While HMB has the potential to adversely affect life from menarche to menopause, societal stigma has led to a lack of awareness and subsequent normalization of symptoms.

Less well described and of greater uncertainty is the impact of antiplatelet therapy on menstrual blood loss. Interestingly, aspirin and other nonsteroidal anti-inflammatory drugs have been hypothesized to reduce menstrual bleeding by inhibiting prostaglandin synthesis, leading to vasoconstriction in the endometrium [5,6]. Yet, aspirin as well as other neurovascular- and cardiovascular-protective agents such as P2Y12 inhibitors increase risk of systemic bleeding due to their antiplatelet effects. With increasing utilization of these agents among women of reproductive age, understanding the effect of antiplatelet therapy on menstrual bleeding remains of critical importance.

In the first systematic review addressing this key question, Kempers et al. [7] reported the effects of antiplatelet therapy on menstrual bleeding among individuals of reproductive age. The authors identified and included 13 studies of menstruating individuals receiving any type of antiplatelet medication, including aspirin, clopidogrel, prasugrel, or other unspecified antiplatelet therapies, in the analysis. Menstrual blood loss was assessed by a variety of methods, including the "gold standard," highly objective alkaline hematin method, and semiquantitative methods such as the pictorial blood loss assessment chart, the modified menstrual pictogram, counts of sanitary items, or other questionnaires or self-perception methods. Included studies used varying comparison groups, including other anticoagulants such as direct oral anticoagulants or vitamin K antagonists, aspirin combined with low-intensity vitamin K antagonists, placebo, or multiple comparison groups. Overall, the included studies were deemed at high risk of bias and demonstrated conflicting results. Two of the 3 studies reporting changes in blood loss volume suggested an increase in menstrual blood loss following initiation of aspirin therapy, especially among those who did not experience HMB prior to treatment [8,9]. Duration of menstruation and flow intensity were also found to be increased, with rates comparable to those randomized to direct oral anticoagulants. Notably, the indication and dosing of antiplatelet medication among the included studies varied widely, from chronic use of low-dose therapy for prevention of cardiovascular disease to high dosages for the treatment of dysmenorrhea during periods of menstruation only. Among the 6 studies involving individuals treated with chronic antiplatelet therapy for primary or secondary cardiovascular disease prevention, HMB was reported in only a minority of participants.

The findings from this systematic review capture the challenges that we face when attempting to synthesize menstrual blood loss data from the available literature. Lack of a consistent and reproducible method of menstrual blood loss assessment and measurement continues to be a major challenge in clinical research. While the alkaline hematin method remains the gold standard for measuring menstrual blood loss and uses spectrophotometry to quantify sample absorbances of menstrual products, barriers to collection and resource

availability have limited the utility of this approach [10]. Alternate approaches through the measurement of menstrual fluid loss or iron/labeled red blood cells, pad counts, or pictorial methods have since been introduced with varying accuracy, discrimination, and ease, though comparative analyses of these methods have been limited [10]. It is clear that standard bleeding definitions used to quantify adverse effects of anticoagulants and antiplatelet medications are insufficient to capture HMB and the psychological impact of its chronic and recurrent nature. Ongoing efforts to standardize assessments of menstrual bleeding and incorporate patient-centric outcomes capturing quality of life are of utmost importance.

Despite widespread use of aspirin for a variety of indications and the fact that 50% of the population will experience menstruation for roughly 40 years of life, there is a paucity of studies describing the effect of antiplatelet therapy on menstrual blood loss. While this may be due, in part, to a lower prevalence of individuals of reproductive age using these medications, perhaps an equal contributor to the lack of recognition is a historical and cultural aversion to discussing menstruation, even among health care professionals [11]. This stigma has led to systemic normalization of symptoms by society and even "medical gaslighting" or the disregard of symptoms by medical providers [11,12]. Large, population-based studies that have attempted to quantify the burden of HMB suggest that nearly half of the individuals experiencing these symptoms have not sought medical attention, and among those who do, evaluation and treatment are often inadequate [2].

The detrimental effects of HMB on health and quality of life have been well described [3,13]. A systematic review evaluating the impact of health-related quality of life suggests that women with HMB consistently score below the 25th percentile of a similarly matched population of reproductive-age individuals [14]. HMB increases susceptibility for and is a key contributor to the development of iron deficiency with and without anemia in those of reproductive age. Iron deficiency is associated with a multitude of adverse effects impacting physical and mental health, including but not limited to fatigue, decreased exercise tolerance, impaired cognition, and maternal and neonatal morbidity [15,16]. While a variety of noninvasive hormonal and nonhormonal strategies exist to manage HMB, at least one-third of hysterectomies performed in the United States are for this indication [17,18]. Based on conservative estimates in 2007, the direct economic burden of HMB approximates $1 billion annually, which includes the costs of physician visits, medications, and treatment of HMB, including hysterectomy [14]. Perhaps the indirect costs of productivity loss and missed work are more challenging to quantify. In fact, approximately 14% to 20% of individuals with HMB report work absenteeism, with a staggering 80% acknowledging presenteeism or productivity loss while being present at work or school [19,20].

Understanding the physical, mental, and economic implications of HMB is essential as we consider the impact of antiplatelet therapy on menstrual bleeding. While effects of antiplatelet therapy on other systemic bleeding symptoms have been described, even in direct comparison with anticoagulant medications, such as in EINSTEIN-CHOICE and AVERROES studies, the age of patients included in these trials was on average 60 to 70 years, and thus, menstrual bleeding was of lesser relevance [21,22]. Studies addressing the detrimental and iatrogenic effects of anticoagulation in the premenopausal population are increasingly growing in number. The TEAM-VTE study, for example, was designed to specifically estimate the incidence, prevalence, and relevance of HMB in a multicenter prospective cohort study of reproductive-age individuals on oral anticoagulants [4]. A staggering two-thirds of individuals met at least 1 criterion for the diagnosis of abnormal uterine bleeding, with a considerable negative impact on quality of life, highlighting the need for growing awareness among providers to take timely action in the diagnosis and management of HMB. Future studies delineating the effects of antiplatelet agents on menstrual blood loss and related impairments to health and quality of life are required for similar risk assessment.

In summary, while there is increasing acknowledgment of the negative impacts of anticoagulants on menstrual bleeding and quality of life, there is still much to be learned regarding the effects of antiplatelet agents. While there are some data to suggest that aspirin may increase menstrual blood loss, the evidence is weak and overall lacking when considering alternate antiplatelet therapies. Importantly, a variety of treatment options exist to reduce the incidence and impact of this troublesome and underrecognized symptom. Ongoing efforts to incorporate menstrual bleeding assessments and patient-relevant outcomes as well as to improve consistency in outcome measures are essential for improving health in this historically marginalized population.

AUTHOR CONTRIBUTIONS

K.L.M. contributed to writing substantial portions of the manuscript. B.S.B. contributed to writing and editing. Both authors reviewed and approved the final manuscript.

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