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CLINICAL TRIALS AND OBSERVATIONS

Comment on de Jong et al, page 1764

The burden of heavy menstrual bleeding

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In this issue of *Blood*, de Jong and colleagues report the first prospective study evaluating abnormal uterine bleeding (AUB) in women beginning anticoagulation for acute venous thromboembolism (VTE), the risk, predictors, impact and outcome of anticoagulation-associated abnormal menstrual bleeding (TEAM-VTE) study.[1] Their findings are striking. Two-thirds of women treated with anticoagulation for acute VTE met the criteria for AUB with a considerable negative impact on their quality of life (QoL). The negative impact of abnormal uterine bleeding, mostly reflected by heavy menstrual bleeding (HMB), on the health and QoL of women and girls with inherited bleeding disorders is well documented.[2,3] However, to date, we have lacked solid data on the prevalence and impact of anticoagulation-associated HMB.

The TEAM-VTE study was an international, multicenter, observational prospective study enrolling women aged 18 to 50 of childbearing potential who were treated with oral anticoagulants for acute VTE. A validated measure of menstrual blood flow (pictorial blood loss assessment chart [PBAC]) and patient perception were assessed retrospectively for the menstrual period before starting anticoagulation and for each menses until discontinuation of anticoagulation or at 6 months, whichever came first. A PBAC of >100 has been correlated with menstrual period blood loss of >80 cc, which is a definition of HMB.[4] Menstrual bleeding-specific QoL (MBQ) was assessed before starting anticoagulation and at the study end. The primary outcome was the overall incidence of AUB during the follow-up period and the incidence of new-onset abnormal menstrual bleeding. Secondary outcomes included impact on QoL.

Overall, 66% of subjects met the definition of AUB at any time in the follow-up period. Three definitions of AUB were used, PBAC >100, PBAC >150, and self-reported AUB, and these were met in 57%, 45%, and 48% of subjects, respectively. In general, subjective reporting of menstrual bleeding correlates weakly with objectively measured blood loss.[5] However, in this study, likely because it reflects a change in menstrual blood flow, self-reported AUB gave results similar to those using PBAC measures and thus could be used in the clinical setting.

The study by de Jong and colleagues documents the impact of AUB on QoL. An increase in MBQ reflects decreased QoL. Overall, the MBQ increased by 5.1 points at the study end in subjects with AUB vs no AUB, and in the group experiencing new-onset AUB, it increased by 9.2 points (new onset AUB vs no AUB). These are dramatic findings and warrant a call to action to define which anticoagulants are associated with less AUB, as well as the optimal treatment for AUB in individuals who menstruate and require anticoagulation. Unfortunately, the study did not meet the enrollment goal and was unable to define risk by anticoagulant. Seven women on dabigatran did not have an increase in menstrual blood flow but also had considerably higher median PBAC scores before anticoagulation.

In addition, the limited data collected did not allow conclusions as to effective treatment of AUB in the setting of anticoagulation. They did not find a significant association between the use and continuation of estrogenic contraceptives at the time of VTE diagnosis and discontinuation of estrogen contraceptives at the time of VTE diagnosis with the occurrence of AUB. However, the confidence interval was wide (odds ratio, 2.24; 95% confidence interval, 0.78-6.4), and more data are needed. Three women had their anticoagulation decreased or stopped, and while they did not experience recurrent VTE during the study, such an approach may carry the risk of recurrence. Lowering the dose of Xa inhibitors during heavy menses has been advocated for the treatment of HMB, particularly after the initial 3 months of anticoagulation.[6] While a lower dose regimen has been shown to be effective in secondary prevention of VTE, it has not been evaluated for efficacy early in the treatment of individuals in whom other reasons for dose reduction are not present.

Only 1 woman in the study by de Jong and colleagues was prescribed tranexamic acid. There are data to suggest that tranexamic acid is safe with anticoagulation, as well as studies of its use in settings that carry a high risk of VTE, which have not reported an increase in

thrombosis with its use.[6] More data on patients on anticoagulation are needed.

The negative impact of AUB on the health and QoL of individuals with inherited bleeding disorders, notably von Willebrand disease and disorders of platelet function, is well documented.[2] AUB is also reported in women and girls with hemophilia A or B and rare factor deficiencies,[3] consistent with an impact similar to what would be seen in those prescribed anticoagulation. HMB impacts physical health by producing iron deficiency, anemia, and the need for treatments that may have side effects. In individuals with bleeding disorders, HMB is documented to have a significant impact on QoL with more days lost from school or work, increased rates of depression, and worse scores using validated measures of QoL compared with individuals without HMB.[2] While useful in identifying individuals with underlying bleeding disorders,[7] in the study by de Jong and colleagues, the International Society on Thrombosis and Haemostasis (ISTH) bleeding assessment tool did not correlate with AUB. However, it may still be useful in screening for underlying bleeding disorders in women and girls with bleeding symptoms in addition to HMB.

Menstrual bleeding has been recommended as a vital sign given its impact on the health and well-being of individuals who menstruate.[8] We must be better at designing studies of anticoagulants that collect prospectively defined data on menstrual blood loss, as well as other reproductive tract bleeding such as hemorrhagic ovarian cysts and secondary postpartum hemorrhage. Recommended definitions of relevant clinical bleeding for use in studies have focused on new bleeding[9] and do not capture well worsening of normal bleeding, such as with regular menstruation.

Further research is needed to define optimal anticoagulant choice and management for individuals who menstruate. For now, when initiating anticoagulation in our clinical practices, we must educate our patients about the risk of heavier menstrual blood loss, ask them about their menses before and after initiating anticoagulation, initiate treatment for HMB as needed, and monitor them for iron deficiency and other associated sequelae.

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HEMATOPOIESIS AND STEM CELLS

Comment on Shin et al, page 1774

Clonal hematopoiesis transcending species barriers

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In this issue of *Blood*, Shin et al expand our understanding of clonal hematopoiesis (CH) by showing its natural emergence in aged non-human primates (rhesus macaques), and by demonstrating robust expansion of *TET2*-mutated clones causing hyperinflammation in a CRISPR-Cas9–based autologous transplantation model in macaques.[1]

CH describes the overrepresentation of the progeny of a single hematopoietic stem cell (HSC), or clone, in the peripheral blood cell pool. A wealth of data published in recent years has established CH as a universal phenomenon associated with human aging.[2-4] Studies have further demonstrated that larger clones bearing leukemia-associated mutations are associated with an array of adverse outcomes in humans, including development of hematologic malignancies and cardiovascular disease[2,5]; this condition has been termed clonal hematopoiesis of indeterminate potential (CHIP) when the variant allele fraction (VAF) exceeds 2%.[6] Murine models have proven to be important tools in understanding underlying mechanisms, indicating that the association of CHIP with inflammatory diseases is causal and a product of increased inflammation in terminally differentiated myeloid cells.[5,7] Embarking on the study presented here, the authors hypothesized that rhesus macaques might present a faithful model organism for CH because they closely resemble humans in many central attributes of hematopoiesis, while still allowing for experimental engineering of CH that would not be ethical in humans.

Out of 60 aged macaques analyzed with a median age of 25 years, 12 were found