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STATE OF THE ART

Tranexamic acid for management of heavy vaginal bleeding: barriers to access and myths surrounding its use

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Abstract

Tranexamic acid is safe and effective for the treatment of heavy vaginal bleeding during menstruation and childbirth. It improves the quality of life, facilitates participation in school and work, and reduces the risk of death from postpartum hemorrhage. Despite its well-established benefits, individual- and structural-level barriers preclude its widespread utilization, hindering effective patient care and perpetuating health inequities in women's health. We first describe the evidence for the use of tranexamic acid in treating heavy menstrual bleeding and postpartum hemorrhage. Barriers to tranexamic acid use, including structural sexism, period poverty, misinformation in product monograph labeling, stigmatization of vaginal blood loss, and drug access, are then discussed. Finally, we summarize relevant data presented during the 2023 International Society on Thrombosis and Haemostasis Congress.

KEYWORDS
heavy menstrual bleeding, postpartum hemorrhage, tranexamic acid, women's health

The authors wish to acknowledge the limitations in the language used in this manuscript to describe those who menstruate, become pregnant, and give birth. The terms "women" and "mother" are deliberately used to highlight the historical and current gaps in knowledge and care for women, though we humbly recognize that this language is exclusive and that these experiences extend to anyone with the anatomy that allows for menstruation, pregnancy, and childbirth [1].

1 | INTRODUCTION

Tranexamic acid was developed by Drs Utako and Shosuke Okamoto, 2 Japanese scientists, in response to the bloodshed of World War II and postpartum hemorrhage (PPH), a leading cause of maternal death in Japan in the 1960s [2,3]. Tranexamic acid is an antifibrinolytic synthetic lysine analog. It competitively inhibits the binding of fibrin to plasminogen and prevents activation of plasminogen to plasmin [2]. Over 50 years later, tranexamic acid is used across multiple medical and surgical domains due to its widespread efficacy in reducing bleeding and safety [2]. Importantly and as predicted by the Okamotos, tranexamic acid is a cornerstone therapy in women's health as it decreases the risk of hemorrhagic death in women with PPH and is highly efficacious for the management of heavy menstrual bleeding (HMB) without increased risk of thrombosis [4,5]. Despite this robust data, misinformation and structural barriers to access preclude its generalized use in the real world.

Heather VanderMeulen and Grace H. Tang are the cofirst authors.

2 | THE PROBLEM: HMB

The prevalence of HMB is estimated between 15% and 61% of all those who menstruate [5]. This broad range reflects the difficulty in accurately measuring and defining HMB. Initial definitions cited menstrual blood loss of ≥80 mL per cycle [6] as excessive, but quantifying menstrual blood loss is challenging. Historically, the alkaline hematin method was used in the research context to estimate blood loss [7]. This is a laboratory-based cumbersome research technique that requires collection and measurement of all menstrual products used and is neither translatable to nor feasible for use in the clinical setting. Rather, clinicians depended on more feasible visual quantitative or semiquantitative measurement methods, including the pictorial blood loss assessment chart (PBAC; which guides visual estimation of blood loss based on the apparent saturation of menstrual products), menstrual cups, and validated Von Willebrand disease Bleeding Questionnaire bleeding assessment tools (BATs) (eg, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 [MDMDM-1], International Society on Thrombosis and Haemostasis [ISTH] BAT) [8,9].

In 2021, the von Willebrand disease guidelines panel adopted more practical and patient-centered definitions of HMB [10]. They define HMB as menstrual bleeding lasting ≥8 days, associated with repeated passing of blood clots, soaking through 1 or more pads/tampons every 2 hours on multiple days, requiring use of >1 pad/tampon at a time, needing to change a pad/tampon overnight, or a PBAC score of >100 [10].

The National Institute for Health and Care Excellence (NICE), American College of Obstetricians and Gynecologists (ACOG), and International Federation of Gynecology and Obstetrics (FIGO) define HMB as excessive blood loss which "interferes with a woman's physical, emotional, social, and material quality of life and which can occur alone or in combination with other symptoms" [11–13]. This definition ties deeply to the principles of believing and validating those with HMB, but qualitative studies of women with heavy vaginal bleeding identified healthcare provider dismissal as a barrier to timely diagnosis and treatment [1,14,15]. Furthermore, while the FIGO definition is intended to be empowering and enabling, its amorphous nature means that it will only be effectively used by clinicians with comfort and skill in identifying HMB and the openness and ability to prioritize this aspect of women's health.

3 | THE EVIDENCE: TRANEXAMIC ACID AND HMB

Access to effective oral therapies is crucial to the management of HMB, but these therapies remain underused [16]. Among 107 women with anatomically normal uteruses referred for hysterectomy for HMB, only 72% had tried an alternative treatment [17]. There is an abundance of literature supporting the use of tranexamic acid as a first-line oral therapy for the management of HMB [18], including a 2018 Cochrane systematic review of 1312 women across 13 randomized control trials [19] and a 2022 Cochrane meta-analysis of 2702 women across 35 studies [5]. Tranexamic acid reduced the amount of blood loss by 40% to 50% for each menstrual cycle [19], translating to an average reduction of 80.32 mL/cycle (95% CI, 32.98-127.67 mL) [5]. Importantly, tranexamic acid also improved health-related quality of life and work participation in those with HMB [19,20]. Therefore, tranexamic acid now represents the standard of care for the first-line oral treatment of HMB. Its use is endorsed by both national and international guidelines [12,21–23]. For this indication, the recommended oral dose of tranexamic acid is 3 to 4 g per day for 4 to 5 days, beginning on the first day of the menstrual cycle [20].

4 | THE PROBLEM: PPH

Globally, PPH remains the leading cause of maternal death and leaves many of those who survive with significant morbidity and "reproductive disability" [24]. Every year, 14 million women suffer from PPH and 70,000 women die from it, though not all women are impacted equally [24]. In the United States, Black women are more than twice as likely to die of PPH than White women [25]. Women in low- and middle-income countries (LMICs), particularly in sub-Saharan Africa, report the highest maternal mortality rates due to PPH, accounting for over 1 in 4 maternal deaths [26]. Contributing factors include poor healthcare infrastructure, high rates of maternal anemia, unreliable access to safe blood for transfusion, and lack of access to prenatal care [27]. Underlying this are widespread gender inequities that result in deprioritization of the health and reproductive rights of women and girls globally [28].

Traditionally, defining PPH was dependent upon the mode of delivery: ≥500 mL of blood loss within 24 hours of a vaginal delivery or ≥1000 mL within 24 hours of a cesarean section [29]. In 2017, the ACOG updated the definition of primary PPH to blood loss of ≥1000 mL with signs and symptoms of hypovolemia within 24 hours of birth [30]. Again, issues pertaining to the accuracy of the diagnosis reach the space of PPH just as they did for HMB. Secondary PPH, defined as abnormal vaginal bleeding between 24 hours and 6 to 12 weeks PPH [29], remains particularly poorly defined and poorly studied.

5 | THE EVIDENCE: TRANEXAMIC ACID AND PPH

The management of primary PPH was revolutionized in 2017 by the findings of the World Maternal Antifibrinolytic (WOMAN) trial [4]. This randomized, double-blind, placebo-controlled trial of more than 20,000 women with PPH compared tranexamic acid 1 g i.v. (plus an additional 1 g i.v. if ongoing bleeding or rebleeding within 24 hours) with placebo [4]. Although there was no significant difference in the composite primary endpoint of mortality or hysterectomy, it showed a reduced risk of death due to bleeding in those who received

tranexamic acid, with the highest impact when tranexamic acid was administered within 3 hours of childbirth (risk ratio [RR], 0.69; 95% CI, 0.52-0.91) [4]. These findings were confirmed by a subsequently published Cochrane systematic review [31]. There was no increase in thromboembolic events among those treated with tranexamic acid (RR, 0.88; 95% CI, 0.54-1.43) [31].

Most of the women recruited to WOMAN lived in Africa (n = 12,343) or Asia (n = 6030), where reported maternal mortality rates in this trial were 3.0% and 1.7%, respectively. In contrast, none of the 1049 women recruited to the trial in Europe died [32]. A qualitative analysis of the narratives of the obstetricians caring for women who died revealed themes of inadequate access to blood transfusion and preexisting anemia [32]. Thus, while tranexamic acid is a critical piece of managing PPH, treatment of anemia in pregnancy and availability of blood for transfusion are critical to saving lives [33,34]. A 2023 cluster-randomized trial assigned 80 hospitals in Kenya, Nigeria, South Africa, and Tanzania to either a multicomponent clinical intervention for PPH (consisting of a calibrated blood-collection drape, first response treatments including tranexamic acid, and training and support for care providers) or usual care. Over 200,000 women participated in the trial, and those who delivered at hospitals assigned to the intervention had lower rates of the combined primary outcome of severe PPH, laparotomy for bleeding, or death due to bleeding (1.6% vs 4.3%; RR, 0.40; 95% CI, 0.32-0.50). This trial demonstrates the importance of early detection of PPH and ready access to treatment, including tranexamic acid, in saving the lives of women in LMICs [35].

Worldwide, guidelines from the World Health Organization (WHO) and FIGO, among others, now reflect the lifesaving role of tranexamic acid in the management of PPH [33,34]. It is listed on the WHO Model List of Essential Medicines [36].

6 | BARRIERS TO TRANEXAMIC ACID

Tranexamic acid is both safe and effective for the treatment of heavy vaginal bleeding during menstruation and childbirth. It improves quality of life, facilitates participation in school and work, and reduces death from PPH. Furthermore, a 2021 systematic review established its cost-effectiveness in treating PPH [37]. Therefore, barriers to its access and use are structural in nature, unfounded in evidence, and largely fueled by sexism, stigmatization of vaginal blood loss, normalization of heavy vaginal bleeding and iron deficiency anemia (IDA), misinformation regarding the risks of tranexamic acid, and inaccessibility in LMICs (see Figure 1).

6.1 | Structural barriers to quantifying vaginal blood loss

Until recently, the true amount of blood contained in various menstrual products was unknown since menstrual products were historically tested using saline [38]. Assessment of modern-day products using expired units of red blood cells (RBCs) showed that the amount of blood held by products varies significantly (2-61 mL) [38]. This makes it exceptionally challenging to quantify 80 mL of menstrual blood loss. In addition, modern products can store large amounts of blood. For example, saturation of 2 heavy pads (100 mL) or 3 heavy tampons (90 mL) over the course of a menstrual cycle qualify as HMB [38]. Thus, if clinicians are relying on frequent product changing to diagnose HMB, they will be missing a significant number of women with HMB [8].

Period poverty refers, in part, to the unaffordability and inaccessibility of menstrual products, which represent a cornerstone in the clinical assessment of HMB [39]. Specifically, period poverty interferes with access to the accepted unit of measure for HMB. This phenomenon is most striking in LMICs but remains a major problem in higher resource settings as well. One in 6 Canadian women has struggled to afford menstrual products [40], and American data suggest that those of low socioeconomic status and those from racialized communities suffer most from period poverty [41,42]. Those unable to access or afford menstrual products are therefore at risk of being unidentified, uninvestigated, and untreated for HMB. In this way, period poverty is self-perpetuating.

Period poverty also describes the reduced workforce and academic productivity in those who menstruate [39]. Those with untreated HMB are more vulnerable to period poverty because they are more likely to miss school or work. With the added cost of absenteeism, HMB perpetuates the negative impacts of ID and anemia as girls and women cannot feasibly attend school/work when bleeding [43]. Unfortunately but not surprisingly, similar challenges extend to our ability to measure PPH. Blood loss at the time of childbirth is measured by visual quantitative or semiquantitative estimation, but current techniques lack correlation with clinically relevant maternal and fetal outcomes [44].

The ACOG definition of PPH is also problematic since it applies the same threshold for blood loss (1000 mL) without consideration for maternal anemia. This puts those with anemia in pregnancy at risk of life-threatening anemia at delivery if they experience PPH. To address this in part, the enrolling WOMAN-2 trial aims to establish the effect of tranexamic acid in preventing PPH in anemic pregnant women [45].

The role of tranexamic acid in the management of secondary PPH is not established because secondary PPH remains poorly defined, and we lack practical methods to screen for it. Measurement of postpartum bleeding after discharge from hospital is similarly confounded by access to pads and period poverty [46].

6.2 | Misinformation: unfounded product monograph warnings

North American (United States and Canada) and European monographs warn providers against using antifibrinolytic agents in those on combined hormonal contraceptives and in those with a history of thrombosis [47–49]. These warnings are not grounded in high-quality

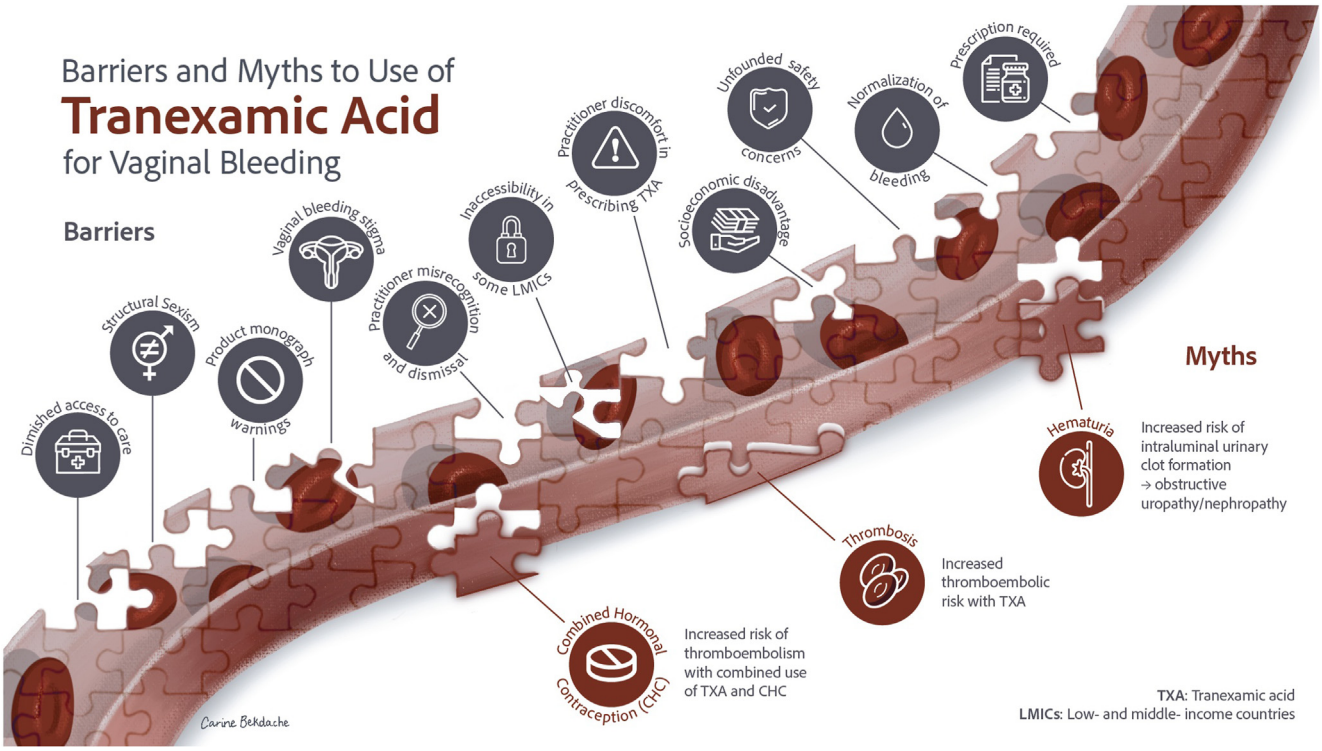

FIGURE 1 Barriers and myths to use of tranexamic acid for vaginal bleeding.

evidence, foster unwarranted anxiety for prescribers, pharmacists, and patients, and perpetuate the following myths:

Myth #1: tranexamic acid causes thrombosis

Despite the hypothetical concern that an antifibrinolytic agent could predispose users to clot formation, tranexamic acid does not cause thrombosis. Mechanistically, this is intuitive since tranexamic acid inhibits fibrinolysis rather than activating coagulation. In a systematic review and meta-analysis of 49,538 nonsurgical patients treated with systemic tranexamic acid, there was no increased risk of deep vein thrombosis (RR, 0.97; 95% CI, 0.69-1.37), pulmonary embolism (RR, 0.97; 95% CI, 0.75-1.26), myocardial infarction (RR, 0.88; 95% CI, 0.43-1.84), or stroke (RR, 1.10; 95% CI, 0.68-1.78) [50]. The evidence is equally reassuring in the surgical population. A systematic review and meta-analysis of 125,550 patients undergoing surgical procedures showed no increased risk of thromboembolic events with tranexamic acid use (RR, 1.02; 95% CI, 0.94-1.11) [51]. Importantly, patients with a history of thrombosis or cirrhosis were excluded from these studies [2]. When used in "generally healthy women" aged 15 to 49 years, a Danish cohort study of 2 million women estimated that the number needed to harm with venous thromboembolism per 5 days of treatment with tranexamic acid is 78,549 [52]. It is worth noting that the thrombotic risk factors of the tranexamic acid recipients in this study were not detailed. Clinicians, thus, should exercise caution when prescribing tranexamic acid to individuals with a recent history of thromboembolism, venous or arterial. However, for the vast majority of patients who experience heavy vaginal bleeding, there is no clear justification to withhold tranexamic acid for fear of thrombosis.

Myth #2: tranexamic acid cannot be combined with hormonal contraception

Medical management of HMB often includes combined oral contraceptive pills (COCs) [53]. Due to their supraphysiologic estrogen content, COCs are associated with a roughly 2-fold increased risk of thrombosis [54], raising concerns about the safety of combining treatment with tranexamic acid. Unfortunately, there is no evidence to definitively estimate the risk of thrombosis in reproductive-aged women using COCs and tranexamic acid together. However, the postpartum period is also a state of high estrogen, and the thrombotic risk in the postpartum period is up to 10-fold higher than that of a nonpregnant woman on a COC. Therefore, the thrombotic risk of tranexamic acid in the postpartum period is a conservative surrogate for the risk of combining tranexamic acid and COC use outside pregnancy, and in this area, the literature is reassuring. A scoping review evaluating the combined effects of antifibrinolytics and either high physiologic or pharmacologic estrogenic states found no clear evidence of increased thrombotic risk [55]. The antifibrinolytic monograph warnings of

thrombosis in combination with COCs are thus founded on low-quality evidence, and prospective trials are desperately needed.

6.3 | Stigmatization of vaginal blood loss and normalization of heavy vaginal bleeding

Due to the limited awareness on HMB among patients and health care providers, coupled with poorly defined methods to quantify blood loss, symptom dismissal is a core theme for women who suffer from HMB [1,15,56–58]. Lending literature from women with bleeding disorders, where HMB is the most commonly reported symptom, contributors to the normalization of HMB can be classified into individual, provider, and societal levels.

On an individual level, patients frequently assess the normality of blood loss by comparing it to their family members and drawing upon their personal experiences [1,15,59]. When those referenced also experience HMB, abnormal bleeding is normalized and continues the intergenerational cycle [1]. In a survey study conducted among women with von Willebrand disease, 71.4% perceived themselves to have "normal" bleeding but, in fact, had clinical measurements consistent with HMB [1,60]. Normalization of HMB can extend to PPH, where individuals are less likely to recognize and, therefore, report secondary PPH. In a qualitative study led by VanderMeulen et al. [59], mothers who experienced HMB minimized their perception of heavy or prolonged postpartum bleeding.

Even when individuals seek medical care, lack of provider awareness in the diagnosis of HMB and inherited bleeding disorders often leads to symptom dismissal. In a qualitative study of women with inherited bleeding disorders (n = 15), all patients reported a degree of symptom dismissal and, for some, experienced tension with their health providers when advocating for further care [15]. Moreover, multiple participants felt their experiences of being dismissed were gendered [15].

At the societal level, the conversation of vaginal bleeding is frequently subject to stigma in various cultures, which in turn amplifies desensitization and maladaptation [1,61]. Given the universal stigma, many simply do not seek medical care for HMB or wait many years from the onset of menarche. In fact, only 4 out of 10 women with HMB will seek medical care, leaving many to suffer silently [62]. The combination of these experiences, coupled with self-doubt and symptom dismissal, perpetuates a cycle of normalization in HMB [58]. Effective knowledge translation strategies are needed to increase HMB awareness, including diversifying the education curriculum to ensure that young women are better informed [58].

Lastly, while a survey of 73 medical trainees found that most recognized the impact of excessive vaginal blood loss (81% "strongly agreed" that excessive vaginal bleeding can negatively impact quality of life), only 1 in 5 were aware of PBACs and only half were aware of BATs [46]. Despite this knowledge gap, this cohort described themselves as largely feeling comfortable with their skills in assessing vaginal bleeding [46]. This highlights excessive confidence in the diagnosis of heavy vaginal bleeding among medical learners and suggests a structural problem in the way we educate the next generation of physicians about vaginal blood loss.

6.4 | The cycle of inequity: iron deficiency, anemia, and bleeding

The conversation of HMB and PPH is incomplete without discussing the risk of ID and IDA. These are inextricably linked themes for women of reproductive age and are increasingly recognized as issues of health equity (Figure 2) [63–66].

When iron losses chronically exceed iron intake due to insufficient dietary iron or ineffective absorption, patients invariably develop ID with or without anemia [67]. This imbalance is magnified for those who experience HMB, as it prolongs the period of iron loss [68,69]. HMB and menstruation-related symptoms are associated with productivity loss and time away from work or school [70]. In a large survey of 32,748 women, menstruation-related symptoms accounted for up to 24% of total absenteeism for women who were working and studying. These findings are likely amplified in those who experience period poverty. The combined impact of HMB and ID/A, which disproportionally affect women and those at vulnerable intersections, negatively impacts their quality of life and impedes their full potential [71].

During pregnancy, ID is the most common cause of anemia due to higher demands of the growing fetus and placenta and maternal RBC mass [72–74]. Adverse outcomes to mothers and their offspring due to low iron stores during pregnancy are well-established and have been linked in more than 1000 published papers. Anemia is associated with placental abruption [75], postpartum depression [76], RBC transfusion [77], maternal death [78], and the composite outcome of severe maternal morbidity or mortality [77]. A meta-analysis by Omotayo et al. [79] reported an increased risk of PPH (odds ratio, 3.54; 95% CI, 1.20-10.40) among those with severe prenatal anemia. Furthermore, maternal anemia has potential implications for long-term child neurodevelopment, contributing to the risk of intellectual disability, autism spectrum disorder, and attention-deficit/hyperactivity disorder [80,81]. Lastly, at delivery, these women experience more PPH and have higher maternal mortality rates [82]. The impacts of heavy bleeding, ID, and anemia span generations.

6.5 | Drug access in LMICs

In addition to the above-described barriers, LMICs may face the added challenge of drug inaccessibility at the time of delivery. One major factor is the high proportion of home births. In sub-Saharan Africa, between 53% and 78% of births occur at home [83]. Since tranexamic acid is most effective for the management of PPH when administered within 1 hour and less effective after 3 hours, women delivering at home in LMICs may miss this critical window for intervention [4].

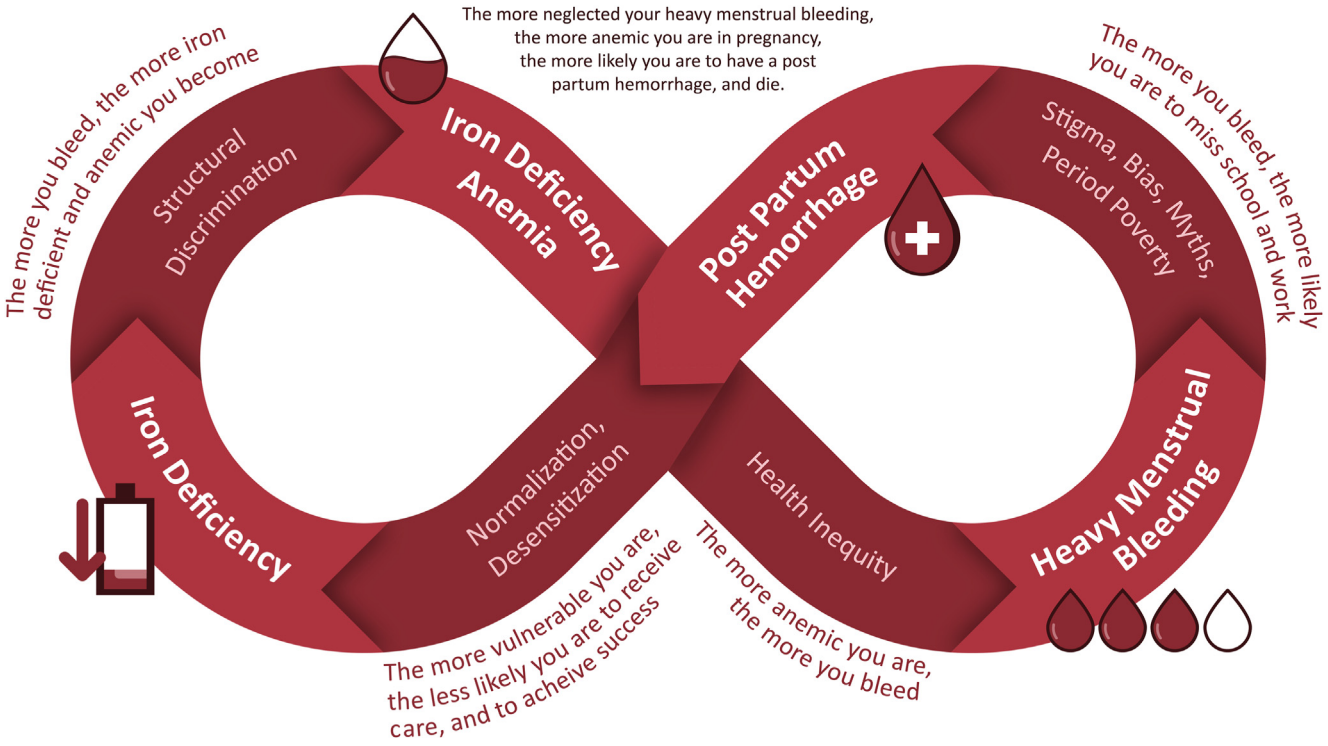

FIGURE 2 Inextricably linked themes for women of reproductive age.

Further, while tranexamic acid itself is relatively inexpensive, there are costs associated with the infusion/injection, including equipment costs and access to a trained healthcare provider [27]. Whether intramuscular administration circumvents some of these barriers and whether oral tranexamic acid has benefits in PPH requires additional study.

7 | FUTURE DIRECTIONS

Numerous opportunities exist to disrupt the cycle of inequity fueled by structural discrimination [84,85]. Utilizing iron supplementation through oral or intravenous routes proves efficacious in treating ID/A [74,86,87]. Similarly, the use of tranexamic acid for HMB or PPH stands out as an effective treatment [20]. However, managing HMB or PPH requires a multifaceted approach that should be centered on actively listening to and believing women of reproductive age when they articulate symptoms of ID and/or HMB. Additionally, effective management entails investigating the root cause that diminishes iron availability and/or elevates iron requirements [84,85]. Ultimately, systemic changes are needed to address the multiple barriers to care, and this requires collaborations between researchers, government, and patient groups. For example, to reduce period poverty, policymakers in several countries including some LMICs have reduced or eliminated taxes on period products [88]. Deliberate resource investment, dedicated research funding, and knowledge translation to promote awareness of ID/A, HMB, and PPH are critically needed. Also, treatment of IDA, a correctable contributor to maternal death and morbidity in women of reproductive age, is listed as a WHO priority for 2025 [89].

8 | ISTH CONGRESS 2023 REPORT

A number of abstracts were presented relating to women's health, in particular HMB and use of tranexamic acid, at the ISTH Congress in 2023.

Maas et al. reported that the prevalence of HMB was 80% (89/111) among individuals with bleeding disorders across 6 hemophilia treatment centers in the Netherlands. Of the 89 women experiencing HMB, 73 sought treatment at some point (82%), with antifibrinolytics being prescribed to only 18 patients (25%). The authors also noted a significant delay in diagnosis of bleeding disorders in women with HMB since menarche, with a median age at diagnosis of 28 years [90].

Findings were supported by Brown and Sidonio who analyzed treatment patterns over a 5-year period in a Young Women's Bleeding Clinic in the United States (104 unique patients over 142 visits). Seventy-eight patients referred (75%) were diagnosed with an inherited bleeding disorder, and of those, 71 (91%) had HMB. The median number of menstrual suppression treatments (including tranexamic acid, COCs, and intrauterine devices) was 3 (range, 1-8), and only 15 patients (21.1%) achieved acceptable menstrual suppression with their first treatment [91].

Lastly, Munireddy et al. reported that 40% (100/251) of women with bleeding disorders experience HMB (as defined by the NICE guidelines) in their United Kingdom cohort. Of these 100 women, 79

(79%) required one or more nonhormonal treatments such as tranexamic acid, desmopressin, or factor concentrate. Importantly, the authors noted inadequate documentation of quality of life (11%; 11/100). Given that the NICE definition of HMB requires an assessment of quality of life, future research is needed to address this care gap [92].

9 | IN MEMORIAM

This manuscript was based on a 2023 ISTH State of the Art talk entitled "Saving Women's Lives Globally with Tranexamic Acid: Barriers to Access and Myths Surrounding Its Use." It is not lost on the authors of this manuscript that structural barriers to care directly prevent the widespread use of tranexamic acid to equitably save women's lives globally. We believe that the Okamotos would be deeply saddened by the existing barriers to use of their wonder drug, tranexamic acid, particularly in LMICs. That said, there are many advances being made to enhance the accessibility and impact of tranexamic acid, which include clinical trials of intramuscular use as well as prophylactic use of tranexamic acid for PPH in those at highest risk of hemorrhagic death (ie, those with antenatal anemia).

This lecture was given in memoriam of Professor Claire McClintock, a self-professed "mother, feminist, art-lover, truth-teller, hematologist, and obstetric physician." To honor her vision and mission, we must collaboratively develop targeted structural solutions rooted in knowledge translation and public health policy to address the multitude of unfortunate gaps in care for women in all parts of the world exposed to the unnecessary risks of heavy vaginal bleeding and secondary IDA. We know we can do it. Together.

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H.V., G.T., and M.S. conceived and wrote the article. All authors provided critical feedback and approved the final version of the manuscript.

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