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Trends in dedicated care for females with bleeding disorders within US Hemophilia Treatment Centers

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To the editor:

Despite significant numbers of female patients affected by bleeding disorders, care at federally funded hemophilia treatment centers (HTCs) historically focused on males. It was not until the mid-20th century that females with a mutation in their factor VIII or factor IX gene were understood to be at increased risk of bleeding (1). Heavy menstrual bleeding (HMB) is the most common symptom experienced by females with bleeding disorders. Yet most bleeding disorder cases among females are undiagnosed due to the lack of awareness. Often bleeding symptoms manifest in the reproductive tract and are often misdiagnosed as a gynecologic problem rather than an underlying bleeding disorder symptom. This, along with stigmatization of menstruation (2), may lead to missed/delayed diagnosis. Given the hemostatic and reproductive challenges inherent in those who menstruate, it is imperative that females with bleeding disorders receive comprehensive interdisciplinary care by experienced healthcare providers.

In 2010, the Foundation for Women & Girls with Blood Disorders (FWGBD), was founded with the mission to correctly diagnose and optimally manage blood disorders and accompanying reproductive problems in females. Comprehensive interdisciplinary clinics, typically consisting of hematology and adolescent medicine or obstetrics/gynecology, serving this unique population have been established over the past few decades and with the launch of FWGBD, are increasing. These clinics are designed to identify females at risk for bleeding disorders, as well as provide optimal management of heavy menstrual bleeding with or without these disorders. Dedicated care for females is also now recommended by international guidelines (3). Here, we seek to describe trends in the establishment of dedicated interdisciplinary clinics, as well as how this care changed the demographics of patients treated within HTCs.

A 22-question survey created by authors in conjunction with colleagues from FWGBD's WGBD Learning Action Network (LAN), was electronically distributed to 81 centers, across all eight U.S. HTC regions. Institutional review board was not required as all data collected is publicly available. Specifically, the survey asked about the range of services offered at each location, focusing on interdisciplinary clinics. Information was collected on clinic hours of operation; clinical specialties and support services offered; patient eligibility; primary clinical complaints; patients' diagnoses; and treatment provided. Surveys were completed by pediatric and adult hematologists, adolescent medicine providers and obstetrician-gynecologists. Centers were asked to qualitatively assess the care their clinic provided compared to external care. The survey link was operated through SurveyMonkey Inc. (San Mateo, CA). Descriptive analyses were performed in SPSS and Excel including one data point per institution.

Hematologists at federally funded HTCs associated with WGBD LAN were contacted and asked to share information regarding the numbers of patients seen in their clinics annually from 2010 through 2020. The data requested was like the report HTCs are required to submit to the

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Hemophilia & Thrombophilia Data Set (HTDS) annually. The HTDS report includes all patients receiving care at their HTC but doesn't include any patient-level information. The total number of patients seen in the clinic by sex assigned at birth, disease type, and age are recorded annually. Descriptive analyses were performed in SPSS and Excel. Pearson's Chi-square test was used to compare trends over time.

Providers from all eight regional hemophilia networks throughout the U.S. responded to the survey and provided HTDS reports (Figure 1); only one HTDS report was accepted per HTC. Thirty-eight providers (46.9%) from unique institutions answered the survey and 18 (22.2%) provided HTDS report data.

Of 38 providers who completed the survey, 34 had established bleeding disorder clinics dedicated to females that included providers in both hematology (pediatric 28, adult 9) and gynecology (pediatric 18, adult 14) or adolescent (9) subspecialities. Some providers care for both pediatric and adult patients and three sites were in the process of establishing clinics. The earliest clinic was established in 2005 (median 2016, mean 2015; range 2005-2020). Dedicated clinics occurred 4 to 36 times per year (median 12, mean 16; range 4-36). Most clinics were half-day with seven lasting a full day. All established clinics provided care for pediatric patients ($\leq$ 18 years old), however fewer clinics served older patients (32 clinics for 19-29 years old, 14 clinics for 30-49 years old, 11 clinics for 50-64 years old and 8 clinics for $\geq$ 65 years old). All clinics provided care for patients with confirmed or suspected bleeding disorders, while fewer provided care for patients with hemoglobinopathies (11/34) and clotting disorders (24/34 clinics). Most clinics provided care for patients with HMB (31/32 responses) while fewer reported caring for patients with hemorrhagic ovarian cysts (6/32), and prothrombotic disorders requiring hormonal therapy or contraception (6/32). A small number of clinics reported care if additional patient populations in written comments, specifically 2 clinics provided care for transgender teens with thrombotic or heavy menstrual concerns and 1 clinic provided care for patients with pregnancy concerns.

Eighteen HTCs provided annual HTDS reports. From 2010 through 2020, the percentage of female patients seen at HTCs increased from 25.9% (n = 850) to 40.3% (n = 3974) (Figure 1A, $p<0.0001$). Of the female patients seen in the HTCs, the percentage of patients with Hemophilia A (9.2% in 2010, 9.6% in 2020)and Hemophilia B (3.1% in 2010, 3.4% in 2020) showed slight variability over the years however did not significantly change over that period. In contrast, the percentage of female patients with von Willebrand disease decreased from 69.3% to 53.9% as the percentage of "other" diagnoses (platelet function disorders, rare factor deficiencies) increased from 15.4% to 33.7% (Figure 1B). From a regional perspective, most regions demonstrated growth in proportion of female patients seen. The number of female pediatric patients also increased from 2010 (n = 334) to 2020 (n = 1969), which represents statistically significant increase in the proportion of female patients in the pediatric age group (Figure 1D, $p<0.001$).

These findings demonstrate a concerted effort over the last decade to provide care for female patients with bleeding disorders at HTCs nationwide. Further, interdisciplinary clinics

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throughout the US have been created specifically to provide care for female-specific bleeding concerns in conjunction with reproductive health colleagues.

These findings are consistent with increasing public awareness and published literature on the evaluation and management of HMB and blood disorders. While the presence of bleeding disorders in females has been acknowledged for decades, there has been an increase in research focused not only on bleeding disorders in females (4), but also a much-needed emphasis on health equity (5). Even the recent American College of Obstetrics and Gynecology (ACOG) definition of HMB is a nod towards acknowledgement of the significant impact of female-specific bleeding (6). Heavy menstrual bleeding is now defined as *"excessive menstrual blood loss that interferes with a woman's physical, social, emotional, or material quality of life*." (7) reflecting quality of life as a more significant and impactful definition, rather than exact milliliters of blood loss. As such, our results reflect this new and sorely needed movement in medicine, focusing on female bleeding as a true medical concern worthy of dedicated interdisciplinary clinics and multifaceted medical management.

As with any survey-based study, there are several limitations. First, any retrospective survey is subject to recall bias. This bias is most prevalent in the survey information collected; however, there were several objective data points (e.g., number of clinics per year) to counter the opinion-based questions (e.g., approximately how many patients do you see per clinic). Specific questions on transgender and pregnancy care were not included so the number of clinics providing this care is likely under-represented. While the HTDS forms provided objective data, this is subject to data entry at each HTC and missing patients are well within the scope of this process. Additionally, some female patients are seen by hematologists outside the HTC setting and are not captured in HTDS forms, thus potentially resulting in an underrepresentation of the female population. Lastly, the survey and HTDS requests were sent to the Hemostasis and Thrombosis Research Society and FWGBD members; these groups are comprised of providers with a vested interest in hemostasis / thrombosis and female bleeding concerns, respectively. Thus, this may represent a biased group compared to the general hematologist population. While we acknowledge the significant shift this may have caused in our results, we feel that new medical movements are often initiated at academic medical centers prior to more widespread acceptance, and we hope that this is the case for the dedicated care of females with bleeding concerns.

This study demonstrates a significant increase in the number of female patients seen in the traditional bleeding disorder clinics (HTCs) as well as individualized interdisciplinary care in dedicated clinics in conjunction with experts in the fields of adolescent medicine and obstetrics/gynecology. Systemic improvement is still needed as many patients and providers likely still do not recognize and refer patients with HMB. The number of female patients with Hemophilia A and B followed within HTCs is still significantly lower than what would be expected given epidemiology/population prevalence of these disorders, and this is likely true of other disorders as well. As this population has historically been marginalized, suffering from missed and/or delayed diagnoses, we are hopeful that this trend will continue and result in further improvements in the care and quality of life of these patients.

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Figure Legend

Figure 1
(A). Hemophilia & Thrombophilia Data Set (HTDS) from Hemophilia Treatment Clinics (HTCs) (n=18): Increasing percentage of female patients were seen at HTCs over the 10-year study period (2010-2020).
(B). Hemophilia & Thrombophilia Data Set (HTDS) from Hemophilia Treatment Clinics (HTCs) (n=18): Among the female patients seen at HTCs the percentage of each diagnosis varied over the course of the 10-year study period (2010-2020).

Figure 2:

(A) Hemophilia & Thrombophilia Data Set (HTDS) from Hemophilia Treatment Clinics (HTCs) (n=18): the absolute number of female patients who were seen in all clinics over the 10-year study period (2010-2020).

(B) Survey data (n=32 as 4 study respondents did not answer what year their clinic opened) demonstrating the absolute number of clinics over the 10-year study period (2010-2020).

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