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LETTER TO THE EDITOR

Issues in reproductive health in females having inherited bleeding disorders in Pakistan

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Women with inherited bleeding disorders, such as platelet function defects (PFD), von Willebrand disease (vWD), haemophilia carrier ship and rare bleeding disorders (RBDs), are vulnerable to severe gynaecological and obstetrical problems with poor quality of life (QOL). They suffer high risk of heavy menstrual bleeding (HMB) and bleeding during pregnancy and childbirth. Pakistan ranks 147 of 188 countries in the world in order of human development index at 0.538 and has a consanguinity rate over 50%. Moreover, Pakistani females suffer from societal pressure to marry and reproduce early, may not seek medical advice for HMB and may remain undiagnosed through lack of disease recognition by health professionals or unavailability of laboratory testing.

This prospective observational study was designed to comprehensively assess gynaecological and obstetric complications and management in women with inherited bleeding disorders in an under-resourced country. It was conducted at a not-for-profit organization, Fatimid Foundation, Karachi (FFK) which has 735 registered patients including 109 (14.8%) females with bleeding disorders. We studied 45 women, aged 12–49 years from January 2015 to January 2016. Clinical data were collected from medical charts on a predesigned questionnaire and included demographic details with personal, family, menstrual, obstetric history, hospital stay and management. Menstrual blood loss was assessed using pictorial blood assessment chart (PBAC) [1]. HMB was defined as changing pads under 2 hours; menstrual bleeding lasting ≥7 days; and the presence of clots >1 cm combined with a history of flooding and a PBAC score higher than 100 according to the ISTH bleeding assessment tool. At our clinic, there is a collaborative team approach with haematologist and gynaecologist consultation and access to factor replacement. Pregnant women were referred to a general hospital for delivery. All data were entered into SPSS version 22.0 (IBM, Armonk, NY, USA). Quantitative data were given as mean (±standard deviation) when normally distributed and median (interquartile range) for non-parametric data. This study was conducted after ethical approval from institutional research ethics committee.

We studied 45 females who were diagnosed at the mean age of 6.5 ± 5.4 years with 34 (75.6%) patients having a positive family history of bleeding. The types of inherited bleeding disorders with bleeding events and management are summarized in Table 1. Overall HMB, dysmenorrhoea, ovarian cysts, miscarriages, primary and secondary postpartum haemorrhage (PPH) were seen in 80%, 55%,44%, 52% and 42% females, respectively, and are in the range of what is reported for women with bleeding disorders from developed countries [2,3].

Heavy menstrual bleeding was a significant complaint in 36/45 (80%) females with a mean age of 26.7 ± 7.6 years, and 34% or 94% had HMB as menarche. HMB was observed in 39%, 50% and 5.5% females with vWD, PFD and RBDs, respectively. HMB with dysmenorrhoea was observed in 24 (53.3%) while isolated dysmenorrhoea and HMB were seen in one and twelve women, respectively. Other bleeding symptoms seen in 32 (88%) females included gum bleeding (n = 28, 78%), epistaxis (n = 27, 75%), bruises (n = 9, 25%) and gastrointestinal bleeding (n = 1, 3%). There were 17/36 (47%) females who visited FFK once or twice every month for HMB with 88% receiving blood components. The median PBAC was high at 160 (range; 100–180). The duration of HMB was 7–15 days, 16–30 days and more than 30 days in 25 (69.4%), 4 (11%) and 7 (19.4%), respectively. Sanitary pads were changed every 2 hours by 28 (77.8%) females. Clots and flooding were experienced by 33 (91.7%) while dysmenorrhoea was experienced by 24 (66.7%) females. Impairment of daily activities with adverse QOL was

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Table 1. Summary of gynaecological and obstetric issues and management in females with inherited bleeding disorders (n = 45).

Bleeding disorders	n (%)	Females with HMB n (%)	Median PBAC score	Total no. of pregnancies (Term/ Miscarriages)	PPH (Primary/ Secondary)	Management* Iron therapy n	Anti-Fibrinolytic n	Hormonal n	Blood transfusion/ clotting factors† n	Surgical intervention n
vWD	17 (37.7)	14 (38.8)	160	12 (5/7)	1 (1/0)	7	13	15	16	1
Type 1	4	4	160	4 (0/4)	–	4	4	4	4	–
Type 3	13	10	150	8 (5/3)	1 (1/0)	3	9	11	12/5	1‡
Presumed vWD§	4 (8.8)	2 (5.5)	160	4 (1/3)	1 (1/0)	1	2	3	4	–
GTT	18 (40)	18 (50)	160	1 (1/0)	1 (0/1)	13	18	18	17	1¶
BSS	2 (4.4)	0	–	4 (4/0)	–	1	1	1	2	–
Hypofibrinogenemia	2 (4.4)	0	–	–	–	–	–	–	2	–
Afibrinogenemia	1 (2.2)	1 (2.7)	140	2 (0/2)	–	–	1	1	1	–
Factor V deficiency	1 (2.2)	1 (2.7)	140	2 (1/1)	1 (1/1)	1	1	1	1	–
Total	45 (100)	36 (100)	160	25 (12/13)	4 (4/2)	23	36	39	43	2

vWD, von Willebrand disease; GTT, Glanzmann thrombasthenia; BSS, Bernard–Soulier syndrome; HMB, heavy menstrual bleeding; PBAC: Pictorial Bleeding Assessment Score; PPH, postpartum haemorrhage.
*Clotting factor concentrates were given in five patients with type 3 VWD.
†This includes transfusion of platelets, cryoprecipitate and fresh frozen plasma.
‡Due to intractable PPH.
§Presumed VWD was based on history of bleeding with prolonged bleeding time and APTT.
¶Due to intractable HMB.

seen in 23 (63.9%) requiring medical attention. Mean haemoglobin in females with HMB was 8.2 ± 2.3 g dL^{-1} with hypochromic microcytic indices indicative of iron deficiency. Ovarian cyst was a significant finding in 10 of 23 (43.5%) females who had pelvic ultrasound with one having haemorrhagic cyst. Tranexamic acid, norethisterone (n = 26) and iron supplementation were the first line of treatment. If bleeding failed to subside, then combined oral contraceptives (n = 16; COC) were prescribed after the discontinuation of norethisterone. Transfusion of platelets, cryoprecipitate and fresh frozen plasma was limited to a maximum of 3–4 units per clotting factor deficient or PFD patient. Patients refractory to tranexamic acid, norethisterone and COC were treated with danazol, as happened in a female with vWD. There were 26/45 (57.7%) females who were unmarried and not sexually active. Despite having no symptoms, four females refused to marry for fear of dyspareunia and PPH. There were 19 married females who had a total of 25 pregnancies with 12 term pregnancies and 13 miscarriages (refer to Table 1). All females had normal vaginal delivery, and there was no bleeding disorder in children.

Studies have reported median PBAC scores ranging from 122 to 215 in females with bleeding disorders in the reproductive age group which is comparable to our PBAC score 160 [2,3]. Using the standardized tool of PBAC, as in our study, HMB was reported in 74–79% women with vWD [2,4]. In contrast, even higher frequency of 93% was reported in type 1 vWD patients using unstructured questionnaire [5]. The prevalence of HMB in vWD varies according to its type with a reported prevalence being higher in type 1 (79–93%) [4,5] compared to type 2 (32–63%) and 3 (56–69%) [6]. Our study shows comparative results with HMB. Besides vWD, HMB is frequently reported in platelet dysfunction such as Bernard–Soulier syndrome (BSS; 51%) and Glanzmann thrombasthenia (GTT; 13–98%) [7,8]. In a prevalence study of 2200 women with HMB, 337 women had bleeding disorders with GTT and BSS reported in 9% and 2%, respectively [9]. In this study, all 18 females with GTT had HMB while two females with BSS did not. Of note, GTT is more frequent in our population than in western countries. Among rare bleeding diseases, HMB was frequently reported in FXI (59%) [10] and FXIII (35–64%) [11] deficiency. However, our cohort included only one factor V deficient and one afibrinogenemia patient and both presented with heavy menstruation. Our study demonstrated anaemia in all patients although 64% were on regular iron therapy. The mainstays of therapy in our clinical practice were tranexamic acid, oral progestogens and COC while levonorgestrel intrauterine device, desmopressin and recombinant factor VIIa were not used due to cost or patient preference. A study on physician practices working in 20 haemophilia treatment centres at United States showed that oral contraceptive (54.5%), desmopressin (34%) and antifibrinolytics (24%) were the common treatment modalities [12]. The low usage of antifibrinolytic in that study was due to its non-availability. The study also highlighted the minimal usage (7%) of blood transfusion [12]. This is in contrast to our study where 64% patients received red cell transfusion for anaemia.

We reported a high rate (44%) of first trimester miscarriages with increased haemorrhage. This is in contrast to very low rate of 5.4% reported from a

neighbouring country – Iran [13] and a little higher 14% reported from USA [12]. There is an increased risk of miscarriages in Factor XIII and fibrinogen deficiency as these clotting factors are required for placental implantation of embryo and the maintenance of pregnancy. We had only one woman with afibrinogenemia, but she had two miscarriages which supports the above explanation. In our cohort, females with vWD had the highest frequency (28%) of miscarriage (general population rate 10–20%).

Antepartum haemorrhage (APH) was not observed in any patient enrolled in the study while PPH was observed in 33% women having vWD, PFD and factor V deficiency. Published reports of PPH in vWD are variable ranging from 6% to 25% [14] and 57% and 43% in BSS and GTT [15]. We believed that the bleeding events in our patients would have been avoided by better communication between obstetricians and haematologists, particularly when they are referred to another hospital for delivery.

This is a first comprehensive study regarding gynaecological and obstetric health problems in Pakistani women with inherited bleeding disorders. However, the small sample size of this study limits our ability to reach generalizable conclusions. Doctors collecting retrospective data on PBAC might have introduced recall bias. The patients were self-selected in virtue of the fact they attended the clinic for management of bleeding during the study period. Hence, they likely represent a more severely affected subgroup of our patient population. This may explain the high rate of complications in our cohort.

Inherited and acquired bleeding disorders in women are challenging for diagnosis and management. The overall frequency of HMB, dysmenorrhoea, ovarian cysts, miscarriages and PPH are within the range of what has been documented in women with bleeding disorders from the developed countries, emphasizing that it is a worldwide issue. Ongoing clinical efforts, research and multidisciplinary approach are required to meet the specific needs of women with bleeding disorders.

Yours sincerely,
Dr. Shabneez Hussain

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Author contribution

SH collected and analysed the data and wrote the original draft of the manuscript. BM reviewed the manuscript, critically analysed the data and provided new ideas to incorporate into the manuscript. SA and NZ helped in collecting the data. All authors approved the final manuscript.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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