RESEARCH ARTICLE

TREATMENT OF FEMALE PATIENTS WITH INHERITED BLEEDING DISORDERS IN REPRODUCTIVE AGE: A SINGLE CENTRE STUDY FROM NORTHERN PAKISTAN

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ABSTRACT

Introduction: *Inherited bleedings disorders (IBD) in women are mismanaged in Pakistan due to lack of standardized treatment options. The most common is Von Willibrand Disease (VWD) followed by rare bleeding disorders (RBD). Heavy menstrual bleeding (HMB) and postpartum hemorrhage (PPH) are the main clinical manifestations causing lot of morbidity and mortality.*

Objective: *To document current treatment practices in female patients in reproductive age with IBD.*

Study Design: *A retrospective study with analysis of patients' records from Hemophilia Treatment Centre (HTC) Rawalpindi.*

Duration: *June 2017 – June 2022*

Place: *HTC, Haemophilia Patient Welfare Society, Rawalpindi.*

Patients and Methods: *Female patients with IBD aged between 11-45 years were included in study. VWD, RBD like deficiencies of factors (I, II, V, VII, X, XI, XIII) and Platelet Function Disorders e.g. Glanzman Thrombesthenia (GTT) and Bernard Soulier Syndrome (BSS) as well as Hemophilia carriers. HMB and PPH were documented along with treatment given.*

Results: *Total 67 patients were included. Age of Menarche was between 11 to 15 years. 89.4% patients with VWD, 60% with RBD and 100% with platelet function defects had HMB. Antifibrinolytic agent was the most common treatment followed by FFP infusion (70 – 86%). Factor replacement was done in 57.5% and OCPs were used in 50% patients. Eleven patients conceived, 10 had full term deliveries and 5 had PPH. They received antifibrinolytics, FFP and factor concentrates*

Conclusion: *In our centre, antifibrinolytics were the most common treatment followed by FFPs, OCPs, hormones and factor concentrates.*

Keywords: *Female patients with IBD in reproductive age, VWD, RBD, Platelet functions defects*

INTRODUCTION

Inherited bleeding disorders (IBD) are a very serious health care issue with lot of morbidity and mortality due to lack of awareness. Inherited Bleeding Disorders are seen in men as well as women. Hemophilia A & B (Factor VIII & IX deficiency) is the most common disorder in males but in women Von Willebrand Disease (VWD) is the commonest.[1] VWD is caused due to deficiency of or abnormality of VWF present in blood,

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which is essential for platelet plug formation. VWF also protects factor VIII in circulation, so its deficiency or absence results in decreased levels of factor VIII. VWD is an autosomal disorder, thus affecting both men and women. There are three types of VWD. Type I and Type II have a autosomal dominant mode of inheritance and are generally mild or moderate in clinical behavior. The most severe form is Type III which is autosomal recessive. Mucocutaneous bleeds are the predominant symptoms but in Type III tissue or joint bleeds may be seen.[1-12] This is the commonest type in Pakistan due to consanguineous marriages.[2] It is very important to correctly diagnose VWD so that appropriate management can be done.

Rare Bleeding Disorders (RBD), are characterized by systemic deficiency of coagulation factors I, II, V, VII, X, XI, and XIII. These disorders are autosomal recessive, therefore due to increased incidence of cousin marriages in our society these disorders are more common here as compared with the west.[2,3] Platelet function disorders like Glanzman Thrombesthenia (GT) and Bernard Soulier Syndrome (BSS) are also seen relatively more frequently here due to the same reason.[4]

Hemophilia is the most well-known and better treated[5] disease which is X-linked and seen in boys mostly.[6] Hemophilia is rare in women. However women who are carriers of factor VIII and factor IX may have varying degrees of bleeding tendency according to the level of factor VIII and IX in them. This has recently lead to categorizing them into a carrier, symptomatic carrier as well as mild, moderate and severe hemophiliacs.[7]

Gene therapy is the latest treatment modality approved for factor IX and VIII and has a considerable impact on the life style of these patient. Although availability to all and morbidity due to viral vector are problems yet to be overcome, it holds a lot of promise to improve the life expectancy of hemophiliacs[8,9] Gene therapy for VWF factor is not available.

The development of treatment of IBDs has made a remarkable improvement in the Quality of Life (QOL) in these patients. Replacement therapy of the missing factor whether human derived or recombinant was a major breakthrough in management of these patients. Availability of factor replacement for treatment of VWD in the developed world plays an important role in improving lives of these patients.[10]

In Pakistan replacement therapy for VWD and other RBD is not readily available so these patients suffers a lot of morbidity and mortality. The mainstay of treatment remains use of blood products like FFP and cryoprecipitate, if available. Adjunctive treatment like antifibrinolytic agent (Tranexamic Acid) as well as oral contraceptive pills (OCP) or hormone based treatment in case of menorrhagia are used mostly.

This study aims to record and categorize the existing state of treatment modalities offered in our clinical setup.

PATIENT AND METHODS

The study was carried out at Haemophilia Treatment Centre (HTC), Haemophilia Patient Welfare Society, Rawalpindi, Pakistan, from June 2017 to June 2022.

Selection Criteria:

Female patients with IBD in age ranged from 11-45 yrs. These include VWD, RBD, (deficiency of factors I, II, V, VII, X, XI, XIII) and functional platelet disorder, Glanzman Thrombasthenia (GTT) and Bernard Soulier Syndrome (BSS).

Age of menarche, treatment modalities in HMB and PPH were recorded after taking proper approval from institutional ethical review board.

RESULTS

This study consisted of total 67 patients having age of menarche between 11-15 years. The breakdown of diagnosis is shown in Fig1. VWD is the most common disease in this group.

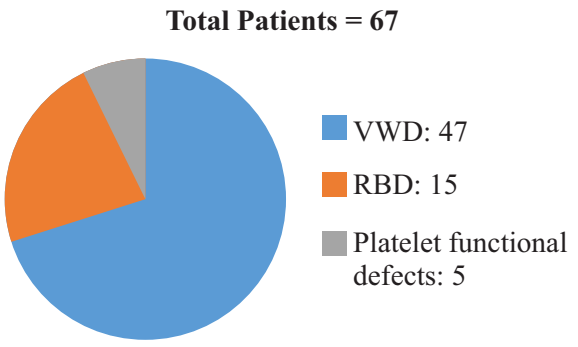

Figure 1: Distribution of patients in three main groups of Bleeding Disorders in Women.

VWD (Von Willibrand Disease), RBD (Rare Bleeding Disorders)

89.4% patients with VWD, 60% having RBD, and 100% with functional platelet disorder reported with heavy menstrual bleeding (HMB).

These patients were managed at the HTC using multiple treatment options available. Antifibrinolytic agent i.e. tranexamic acid was the mainstay of treatment followed

Table I: The different treatment modalities used in our patients for HMB. Received 'R', Not Received 'NR'. OCP (Oral Contraceptive Pill), FFP (Fresh Frozen Plasma)

DISEASE	TOTAL PATIENTS	TREATMENT RECEIVED									
		Antifibrinolytics		OCPs/Hormones		FFP		Factor Concentrates		Platelets	
		R%	NR%	R%	NR%	R%	NR %	R%	NR %	R%	NR %
VWD	47	91.5	8.5	57.5	42.5	70.2	29.8	57.5	42.5	-	-
RBD	15	60	40	40	60	86.6	13.4	-	-	-	-
Platelet functional defects	5	100	0	40	60	-	-	-	-	40	60

by FFP infusion in more serious bleeds. Factor replacement was done in 57.5% patients only. OCPs were used in nearly half the patients. Table I shows the details of treatment in our patients.

Outcome of Pregnancy

Total of 11 patients conceived, 5 patients had PPH and 4 delivered without any complication among total of 9 patients having VWD. There were 2 patients having RBD who conceived without any complaint of PPH. One patient had abortion in previous pregnancy in first trimester. Factor concentrate, antifibrinolytic agent and blood products were administered to these patients. They were delivered in Govt Hospitals (PIMS, BBH). Treatment plan was given by HTC. These patients received factor concentrates, blood products (FFP and Cryoprecipitate) and transmine. Table II gives details of Pregnancy Outcome in this study.

Table II: Pregnancy outcome in eleven patients.

PPH (Post-Partum Hemorrhage)

	Number of patients	PPH	Abortion	Normal Delivery
VWD	9	5	Nil	4
RBD	2	0	1	2

DISCUSSION:

The spectrum of inherited bleeding disorders in women reveals VWD to be the commonest [11] followed by Rare Bleeding Disorders (RBD) which are deficiencies of factors I, II, V, VII, X, XI, XIII. These disorders are mostly autosomal recessive and, thus higher incidence of these disorders in some ethnic groups is seen due to cousin marriages.[2,12]

The clinical signs and symptoms due to bleeding are similar in men and women with addition of menstrual blood loss and excessive bleeding during childbirth in women. HMB is important cause of morbidity impacting the lives of young girls causing psychosocial issues. The incidence of post-partum haemorrhage (PPH) is high in these women, causing increased morbidity and even mortality if not properly managed.[12]

Hemophilia is the most well managed bleeding disorder. For both hemophilia A and B, Factor Replacement Therapy, plasma derived and recombinant coagulation factor concentrate (CFC), is available. Novel therapies like emicizumab and gene therapy are also available now making the lives of hemophiliac fairly comfortable. Hemophilia carriers, who are women have varying degree of bleeding symptoms according to their levels.[7] Treatment of VWD in the west has improved Patients Quality of Life.[10-13]

There is a limited experience of treatment of female patients with VWD and RBD in Pakistan due to lack of awareness and poor facilities. Recommendations for treatments of women affected with these disorders are available for guidance and reference.[10]

In rare Bleeding Disorders the recommended treatment is replacement of the missing coagulation factor. However, in case of minor bleeds using adjuvants like antifibrinolytic only can be effective to control bleeding.[14]

Specific recombinant therapy is available for factor VII and factor XIII in the west whereas no specific factor replacement therapy is available for FII and FV deficiency.[14]

In Pakistan only factor VII concentrates are available but are very expensive so not affordable. Therefore the

mainstay of treatment is use of fresh frozen plasma or cryoprecipitate as appropriate. Our study shows use of FFP in 70 – 86% patients as CFCs are not freely available.

A very useful adjuvant to specific factor replacement therapy is antifibrinolytic like tranexamic acid. Mild Bleeding symptoms are usually controlled by conservative measures like use of ice packs, compression bandage elevation of limb, rest (RICE) and addition of transmine.[15] Our study shows use of transamine in 60 – 100 % patients to control bleeding.

The use of oral contraceptive pills (OCPs) is an effective way of managing menorrhagia. This is used in young women to stop menstrual cycles and thus control HMB by continuous uninterrupted use of OCP.[11,12&15]

The number of female patients with platelet functional defects like GTT and BSS is very low. The mainstay of treatment was platelet transfusion (40%) and transamine (100%) .[4]

We have a very limited experience of dealing with pregnancies in women with IBD. Our study identified eleven patients who conceived. The results of delivery show relatively better outcomes. This shows the importance of identifying these patients so that they are guided and supported during pregnancy and puerperium.

However, the lack of awareness and diagnostic facilities for bleeding disorders results in adverse outcomes of pregnancies or maternal fatalities due to mismanaged PPH.

CONCLUSION

Antifibrinolytics, FFPs and hormones are the primary treatment in our clinical facility followed by factor concentrate, which are not freely available.

Conflict of interest:

None

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