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RESEARCH ARTICLE

The Association of ABO RH Typing and von Willebrand Factor Levels in Reproductive-Aged Women with Abnormal Bleeding Tendencies; A Case-Control Study in Ghana

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Abstract

Background: Reproductive-aged women often experience bleeding episodes such as heavy menstrual bleeds, abnormal uterine bleeds, post-partum bleeds, and epistaxis, which may threaten their well-being. The presence of an underlying bleeding disorder such as von Willebrand disease (vWD) may aggravate the situation. ABO blood group has been known to influence the levels of vWF but the mechanism is not fully understood. This study was aimed at determining the association of vWF and ABO RH blood groups among these reproductive-aged women with abnormal bleeding episodes. **Materials and Methods:** This was a case-control study involving 90 women of reproductive age: 30 with history of abnormal bleeding and 60 controls. Venous blood sample was collected for ABO Rh blood typing, complete blood count (CBC) analysis and plasma vWF level determination. The data was captured with Microsoft excel version 2016 and analysis done with SPSS version 26. Statistical significance was set at $P<0.05$. **Results:** The vWF antigen level in participants with a bleeding history were lower than that of those without a bleeding history ($p= 0.002$). The blood group with the highest distribution among the study population was O Rh (D) positive. Blood group B Rh (D) positive recorded significantly higher levels Ag level of vWF ($p=0.032$). **Conclusion:** Plasma vWF levels in the study subjects were determined to be influenced by their ABO blood group antigens**.** Persons with blood group O recorded the lowest levels of vWF. The differences in vWF levels among the A, B, and AB blood groups were statistically insignificant. Reproductive-aged women with a history of abnormal bleeding had significantly lower levels of vWF antigen, as well as those on contraceptive medications.

Keywords: Bleeding Tendencies, Von Willebrand Factor, Blood Group, Reproductive-Aged Women.

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1. Introduction

Bleeding disorders encompass a diverse range of conditions, varying from mild bleeding symptoms to severe and occasionally life-threatening bleeding manifestations. Given the normal occurrences of bleeding during the reproductive years, women with even mild bleeding disorders are prone to experiencing abnormal bleeding tendencies that may be inherited or acquired (Presky & Kadir, 2020). Women in their reproductive years are frequently affected by inherited bleeding diseases such as von Willebrand disease (vWD), inherited platelet disorders, and rare syndromes such as factor VII (FVII) insufficiency and factor XI (FXI) deficiency (Winikoff *et al*., 2019).

Von Willebrand disease (vWD), the most common genetic bleeding condition, is identified by bleeding in the mucocutaneous region (Sabih & Babiker, 2017) such as profuse menstrual bleeding, nosebleeds, skin bleeds, and bleeding gums. This disease can be categorized into three types, based on the deficiency in either the quantity or quality of the von Willebrand factor (vWF). Type 1 vWD, which accounts for 70-80% of all vWD cases, is distinguished by lower levels of vWF. Type 2 vWD, which affects around 20% of vWD patients, is differentiated by aberrant vWF functionality. The absence of vWF distinguishes type 3 vWD, which affects less than 5% of people. Types 1 and 2 vWD normally follow an autosomal dominant pattern, whereas type 3 vWD is an autosomal recessive condition (Atiq *et al*., 2021). The general populace has a prevalence rate of 1% to 2% for vWD. Moreover, the occurrence of von Willebrand disease differs across diverse populations. Many studies have primarily focused on assessing the prevalence of vWD in European and American countries among women experiencing menorrhagia, with limited reports from Asia. In Ireland, the prevalence of vWD was found to be 13% (Woo *et al*., 2002), while in the UK it was also 13% (Kadir *et al.*, 1998; Abdoli *et al.*, 2020). Sweden reported a prevalence of 20% (Edlund *et al.*, 1996), whereas in the USA, it ranged from 5.1% to 17% (Philipp *et al.*, 2003). In Taiwan, the prevalence was reported to be 16.1% (Chen *et al.*, 2008; Abdoli *et al*., 2020). A study in Nigeria found that vWD occurrence among young people in Nigeria was 2.2% (Shonde-Adebola *et al*., 2021).

Von Willebrand factor however, is the most abundant glycoprotein found in the bloodstream, responsible for regulating the adhesion and clustering of platelets (Zeng *et al*., 2022). It serves two main roles in the process of blood clotting. Firstly, it aids in the adherence of platelets to the endothelium of blood arteries, hence enhancing interactions between platelets and facilitating their aggregation in vessels experiencing high shear stress. Secondly, vWF acts as a carrier for coagulation factor VIII (FVIII) in the bloodstream, safeguarding it from deterioration by enzymes, extending its lifespan in circulation, and effectively directing it to the specific site of vascular injury (Shonde-Adebola *et al.*,2021). To carry out its intended role, vWF must form extensive, disulfide-linked multimers of significant size (Zeng *et al*., 2022). The diverse molecular weights of vWF are attributed to variations in terms of the number of subunits forming the protein. However, it is only the largest multimers that exhibit haemostatic activity. Within each vWF subunit, there are specific sites that bind to collagen as well as platelet glycoproteins GPIb and GPIIb/IIIa (Furlan, 1996). Plasma levels of vWF exhibit considerable variation both within individuals and among different individuals. These fluctuations have been linked to various factors such as ABO blood type, race, oestrogen levels, age, and stress. Notably, ABO blood type has a significant influence on the levels of vWF in the plasma (Shonde-Adebola *et al*., 2021).

The ABO blood group antigens, which occur on the surfaces of red blood cells (RBCs), have been widely examined and represent the most well-documented and genetically varied blood type system out of the 300+ distinct blood group antigens discovered (Rehman et al., 2022). Despite the presence of the A, B and H determinants, which form the ABO blood group system being associated with red blood cells, they can also be present on various cell types such as platelets, von Willebrand factor (vWF), and endothelial cells (Appiah *et al*., 2022). While the precise role of ABO blood group antigen remains unclear, von Willebrand factor provides insight into their function. According to Matsui and Nakamura, von Willebrand factor bears the ABO blood group antigens and its amount in the bloodstream is affected by a person's ABO blood type, and individuals with blood type O typically have roughly 25% lower levels of vWF compared to those with blood types other than O (Matsui & Nakamura, 2020). ABO (H) determinants are found on both the N- and O-linked glycans of human plasma-derived vWF. Although the H antigen is present on vWF produced from platelets, the A and B antigens are not (McGrath et al., 2010; McGrath *et al.*, 2013). The presence of ABO (H) antigens on vWF is critical for

controlling several aspects of vWF biology. First of all, it lowers the amounts of the vWF-FVIII complex in the plasma, which explains why persons with blood type O have lower levels than other blood groups. This difference is most likely due to greater clearance of vWF in blood group O individuals. Furthermore, ABO expression on vWF impacts its susceptibility to proteolysis by ADAMTS13, with a considerably greater rate of cleavage in persons with blood group O. Recent research reveals that ABO antigens on vWF influence its functional ability to interact with platelet GPIb. (O'Donghaile *et al*., 2020).

Even though vWF is a very crucial haemostatic protein, there is a paucity of data about its association with ABO blood groups among Ghanaian women with abnormal bleeding episodes population. As a result, the purpose of this study is to evaluate the plasma levels of vWF and assess its relationship to ABO blood antigens in reproductive-aged females with a history of bleeding in Tamale, Ghana.

2. Materials and Methods

2.1 Study Design/Site

This was a case-control study that took place at Tamale in the Northern region of Ghana among reproductive aged women at the University for Development Studies, from June 2023 to November 2023. The Northern region is one of the 16 administrative regions in Ghana, and it currently ranks as the second largest and fifth most populous region among these administrative divisions, comprising approximately 7.5% of Ghana's total population of 30.8 million people. The gender distribution in the region is nearly balanced, with 49.4% males and 50.6% females. Islam is the predominant religion practiced in this region. The population density is approximately 87.1 individuals per square kilometre. Geographically, the region is situated at latitude 9° 29' 59.9" N and longitude -1° 00' 0.00" W, with Tamale serving as its administrative capital. The establishment of UDS was authorized by the Ghanaian government through Provisional National Defense Council (PNDC) law 279, and it was officially gazetted on May 15, 1992. Notably, this research will specifically take place on the Dungu campus of the University (Kanton *et al*., 2023).

2.2 Ethics and Human Subject Issues

The Institutional Ethics and Research Committee of the University for Development Studies, Tamale, Ghana granted ethical clearance for good clinical practice (UDS/RB/062/23). The sampling facilities provided certifications for the study. Before consideration and participation in the study, each subject received a thorough description of the study and signed an informed consent form.

2.3 Study Population/Sample Size

This study involved 90 consenting females in their reproductive ages, 30 participants with a history of abnormal bleeding (cases), and 60 without a history of abnormal bleeding (controls).

2.4 Inclusion and Exclusion Criteria

The study included individuals aged 15 to 49 years with history of abnormal bleeding. Those below 15 years or above 49 years, as well as individuals with acute conditions like malaria or chronic illnesses such as hypertension, diabetes, and sickle cell disease were excluded from the study. Additionally, individuals taking medications like aspirin and pregnant women were also excluded.

2.5 Sample Collection and Processing

Five millilitres of venous blood samples were obtained from participants using vacutainer needles, 3 ml of sample was put into sodium citrate tubes and used for vWF antigen level assay. About 2 ml of the sample was placed in K3EDTA sample tubes and was used for complete blood count analysis and ABO/Rh blood typing.

The sample in the sodium citrate tube was span at 3000rpm for 15 minutes using a centrifuge (SM80-2, Microfield instrument, England) and plasma was separated into plain tubes, and stored in a freezer at a temperature of -20˚C. This was done within two hours after sample collection.

Complete blood count was carried out on the K3EDTA sample within 2 hours of sample collection, using a fully automated haematology analyser (BC-2800, Mindray, China). Blood typing was carried out using commercially prepared monoclonal antibodies for the A, B, and Rh D antigens on the EDTA blood using the standard tube method for blood grouping.

2.6 Complete Blood Count Analysis

The CBC was performed using a fully automated haematology analyser (BC-2800, Mindray, China) that operates on the Coulters principle of impedance and spectrophotometry for haemoglobin determination. The blood cells are counted by forming an electric field surrounding a calibrated micro aperture through

which the blood cells flow after being diluted in an electrolytic diluent. The lysing reagent converts all haemoglobin derivatives (Hb (haemoglobin), MetHb (methaemoglobin), and HbCO (carboxyhaemoglobin) to HiCN (cyanmethaemoglobin), and the absorbance is measured at 540nm.

2.7 Blood Group Determination

Blood group typing was carried out using commercially prepared monoclonal antibodies for the A, B, and Rh D antigens on the EDTA blood sample using the standard tube method for blood grouping.

Red blood cells were washed three times with normal saline and a 3-5% cell suspension was prepared after the third wash. Two drops of cell suspension are put into each of three test tubes labelled, A, B, and D. A drop of each of the antisera A, B, and D are added to the corresponding tubes labelled A, B, and D and gently mixed. The tubes were incubated at room temperature for 15 minutes and observed for agglutination. If no agglutination is observed, they are centrifuged at 1500rpm for 1 minute and agglutination is observed with the naked eye or under the microscope.

If agglutination is observed in any of the tubes, it gives an indication that that particular antigen is present in the sample. If no agglutination is observed, then it indicates that the antigen is absent in that sample.

2.8 Von Willebrand Factor (vWF) Assay

Purified human vWF antibody is used in the kit to coat microtitre plate wells, create solid-phase antibody, and then add vWF to wells. It combines VWF antibody with HRP labelling to form an antibody-antigen-enzyme-antibody complex. After thoroughly cleaning, TMB substrate was added to the solution. The TMB substrate turns blue. The HRP-catalysed process is stopped by adding a sulphuric acid solution, and the colour change is detected spectrophotometrically at 450 nm. The optical density of the samples is then compared to the standard curve to determine the concentration of human vWF in the sample.

2.9 Statistical Analysis

Data was collected with Microsoft Excel 2016 and analysed into an IBM statistical package for social sciences (SPSS) version 26. Dependent and independent variables were assessed to determine the strength of association with the use of Chi-Square for categorical data. Categorical data were summarized and given in frequencies, with equivalent frequencies in parenthesis. Non-parametric data were presented as Median with 25th-75th percentiles in parenthesis. The Independent T-Test was used to compare parametric data, whereas the Mann-Whitney U-Test was used to examine non-parametric data. The Kruskal Wallis H-test was used to compare three or more sets of data having non-parametric distribution. Figures and tables were used to present data. All statistical tests were considered significant if $P< 0.05$.

3. Results

Table 1. *Demographic and Clinical Characteristics of the Study Participants*

		Total(N=90) Participants	
		With Abnormal Bleeding History (n= 30)	**Without Bleeding History (Controls) (n=60)**
Age category(years)	<20	22 (73.3%)	8 (13.3%)
	>25	1 (3.3%)	5 (8.3%)
	20-25	7 (23.4%)	47 (78.4%)
Ethnicity	Mole-Dagbani	27 (90.0%)	42 (70.0%)
	Others	3 (10.0%)	18 (30.0%)
Are you on contraceptives?	Yes	4 (13.3%)	0 (0.0%)
	No	26 (86.7%)	60 (100.0%)
Do you get abnormal bleeds?	Yes	30 (100.0%)	0 (0.0%)
	No	0 (0.0%)	60 (100.0%)
Specify where you bleed	Nose	6 (20.0%)	0 (0.0%)
	Gum	17 (56.7%)	0 (0.0%)
	Nose and Gum	3 (10.0%)	0 (0.0%)
	Vagina	4 (13.3%)	0 (0.0%)

Table 1: categorical data is shown as frequencies, with percentages in parenthesis.

3.1 Demographic and Clinical Characteristics of Study Participants

Table 1 shows the study participant's demographic and clinical characteristics. With the ages of those with bleeding history, 22(73.3%) were less than age 20 years, 1(3.3%) was above age 25 years and 7(23.4%) between the ages of 20-25 years. Also, 27(90.0%) of them belonging to the Mole-dagbani ethnic group and 3(10.0%) belonged to other ethnicities. Out of this population, 4(13.3%) were on contraceptives and 26(86.7%) were not. All the participants with bleeding history experienced abnormal bleeds and with the specification of bleeding sites, 6(20.0%) bleeds from the nose, 3(10.0%) bleeds from both the nose and gum, 4(13.3%) get prolonged menstrual bleeds and 17(56.7%) bleeds from the gum. The participants without bleeding history had 8(13.3%) of them with age less than 20 years, 5(8.3%) had their ages above 25 years and 47(78.4%) had their ages between 20-25 years. The ethnicity of this population comprised of 42(70.0%) of them belonging to the Mole-Dagbani ethnic group and 18(30.0%) belonged to other ethnicities.

3.1.1 Comparison of Haemogram Parameters among Reproductive-Aged Women with abnormal bleeding history and controls (no bleeding history)

The median haemogram indices of women with abnormal bleeding :TWBC x$10^9$$10^9$/L [3.37 (2.51-3.84) vs 2.55 (1.64-3.34), p= 0.004]; {LYM# x$10^9$$10^9$ /L [1.86 (1.40-2.24) vs 1.10 (0.85-1.89), p=<0.001]; MCHC g/dl [37.70±1.90 vs 36.0±1.40, (p<0.001)], PCT% [0.37±0.02 vs 0.27±0.02, (p=0.001)], MPV (fL) [10.80±1.40 vs 10.80±1.40, (p<0.001)], P-LCR[31.80±11.50 vs 20.4±10.2,(p<0.001)] were significantly higher than the participants without bleeding history (controls) as shown in Table 2.

Table 2. *Comparison of Haemogram of Reproductive Women with Abnormal Bleeding History and Controls (No Bleeding History).*

Variable	Total (n=90)		*p-value*
	With Abnormal bleeding history (n=30)	No bleeding history (n=60)	
TWBC x$10^9$$10^9$/L	3.37 (2.51-3.84)	2.55 (1.64-3.34)	0.004
LYM#x$10^9$$10^9$/L	1.86 (1.40-2.24)	1.10 (0.85-1.89)	<0.001
MID#x$10^9$$10^9$/L	0.22±0.08	0.21±0.12	0.368
GRAN#x$10^9$$10^9$/L	1.21 (0.85-1.89)	1.00 (0.55-1.45)	0.129
RBC (10^{12}/L)	3.88±0.40	3.96±0.47	0.414
HGB (g/dL)	12.70±1.70	12.6±1.40	0.723
HCT (%)	33.90±3.80	34.9±3.40	0.178
RDW-CV (%)	14.70±1.60	15.0±1.20	0.464
MCV (fL)	88.10±10.30	89.4±8.00	0.531
MCH (pg)	33.30±4.30	32.3±3.20	0.238
MCHC (gdL)	37.70±1.90	36.0±1.40	<0.001
PLT (10^9/L)	334.00±112.00	294±115.00	0.114
PCT (%)	0.37±0.02	0.27±0.02	0.001
MPV (fL)	10.80±1.40	10.80±1.40	<0.001
PDW (fL)	16.50±0.90	16.2±0.8	0.091
P-LCR	31.80±11.50	20.4±10.2	<0.001

Table 2: *n=Number of participants, TWBC=Total white blood cell count, LYM# =Absolute lymphocyte count, GRAN# = Absolute granulocyte count, MID# =Total of WBCs not categorised as LYM or GRAN, RBC=Total red blood cell count, HGB=Hemoglobin concentration, , HCT=Hematocrit, RDW-CV=Red blood cell distribution width-coefficient of variation, MCV=Mean cell volume, MCH=Mean cell hemoglobin, MCHC=Mean cell hemoglobin concentration, PLT= Platelet count, PCT= Plateletcrit, MPV=Mean platelet volume, PDW=Platelet distribution width. P-LCR= Platelet larger cell ratio Parametric Data is shown in mean ± SD while non-parametric data is presented in Median (25th-75th percentile). The Independent T-Test was used to compare parametric data, and the Mann- Whitney U-Test was used to examine non-parametric data. P-values less than 0.05 were considered significant, whereas p-values more than 0.05 were judged non-significant.*

3.2 vWF Antigen Levels among Reproductive Aged Women with Abnormal Bleeding Tendencies and Controls

Figure 1 illustrates the vWF antigen levels stratified by reproductive aged women with abnormal bleeding history and controls (those without abnormal bleeding history). The median vWF Ag. levels of the total population were 57.28 (42.66-83.84) IU/L. The median vWF Ag. level of the participants with abnormal bleeding history was 46.74 (28.84-59.31) IU/L and that of those without bleeding history was 65.98 (46.79-88.93) IU/L. vWF antigen levels in participants with no bleeding history were significantly higher than that of those with bleeding history (p= 0.002).

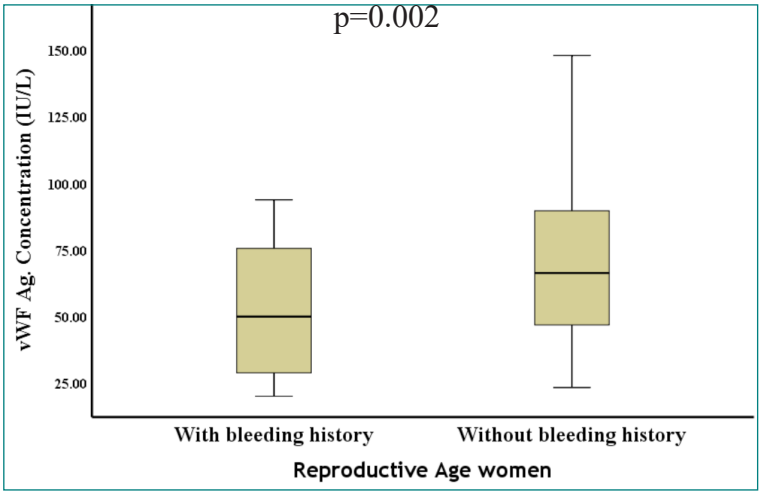

Figure 1. *vWF Ag. levels stratified by study participants. vWF= von Willebrand Factor, Ag. conc= Antigen concentration, IU/L= international units per litre. Data were compared using Mann- Whitney U-Test. p-value=<0.05 was considered significant.*

3.3 Distribution of ABO and RH (D) Blood Groups among Study Participants

Table 3 shows the distribution of the various blood groups among reproductive aged women with bleeding history and controls (those without bleeding history). Out of the participants with bleeding history, 6(20.0%) were A Rh(D) positive, 7(23.4%) were B Rh(D) positive, 4(13.3%) were AB Rh(D) positive, 13(43.3%) were O Rh(D) positive and none of them was O Rh(D) negative. Amongst those participants without bleeding history:12(20.0%) were A Rh(D) positive, 11(18.3%) were B Rh(D) positive, 3(5.0%) were AB Rh(D) positive, 32(53.4%) were O Rh(D) positive and 2(3.3%) were O Rh(D) negative as shown below. Blood group O Rh (D) positive had the highest distribution among the study population.

Table 3. *Distribution of ABO and RH (D) Blood Groups among Subjects*

BLOOD GROUPS	Reproductive Age women			
	With abnormal bleeding history		Without abnormal bleeding history	
	Frequency	%	Frequency	%
A Rh(D) positive	6	20.0	12	20.0
B Rh(D) positive	7	23.4	11	18.3
AB Rh(D) positive	4	13.3	3	5.00
O Rh(D) positive	13	43.3	32	53.4
O Rh(D) negative	0	0.0	2	3.3
TOTAL	**30**	**100**	**60**	**100**

Table 3: distribution of blood groups among participants is shown as frequencies with the corresponding percentages.

3.4 Variation of vWF Antigen Levels and Blood Groups among Study Participants

Figure 2 illustrates variation of the median levels of vWF Ag amongst the various blood groups in the study participants. The median Ag level of vWF of those with blood group A Rh(D) positive [57.56 (46.16-92.74) IU/L], B Rh(D) positive [75.20 (40.31-99.83) IU/L], AB Rh(D) positive [51.52 (31.65-87.98) IU/L], O Rh(D) positive [51.31 (39.43- 66.57) IU/L] and O Rh(D) negative [65.05 (57.82-86.98) IU/L] with (p= 0.032).

Blood group B Rh (D) positive however, recorded the highest median Ag level of vWF with blood. The following were the p-values amongst the various blood groups; between A Rh(D) positive and B Rh(D) positive p= 0.995, between A Rh (D) positive and AB Rh(D) positive(p=0.889), between A Rh(D) positive and O Rh(D) positive (p=0.227), between A Rh(D) positive and O Rh(D) positive (p= 0.997), between AB Rh(D) positive and B Rh(D) positive (p=0.536), between AB Rh(D) positive and O Rh(D) positive (p=0.984), between AB Rh(D) positive and O Rh(D) negative(p= 0.991), between O Rh(D) positive and B Rh(D) positive (p=0.025), between O Rh(D) negative and B Rh(D) positive p=0.959, between O Rh(D) negative and O Rh(D) positive (p=0.889).

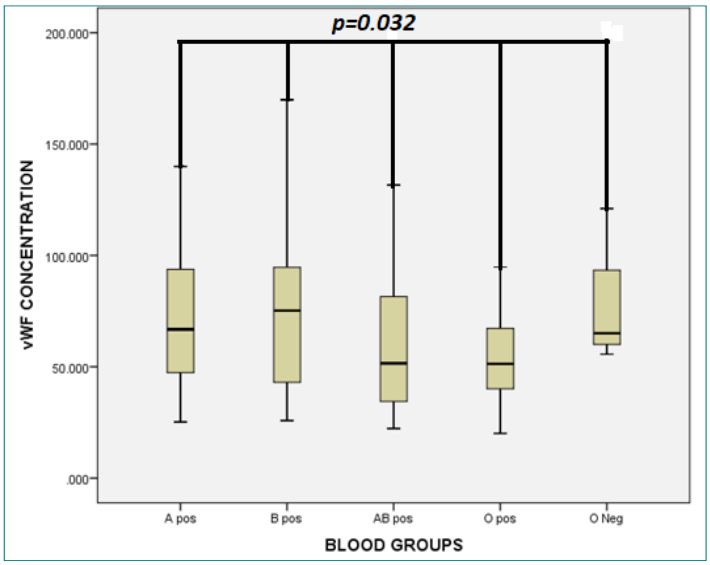

Figure 2. *Variation in the Levels of vWF Ag and Blood Groups among Study Participants. vWF= von Willebrand Factor, Ag. conc= Antigen concentration, IU/L= international units per litre. Data were compared using Kruskal Wallis H- Test was used. p-value >0.05 was considered significant.*

3.5 Variation in Levels of vWF Antigen and Blood Groups among Participants without Abnormal Bleeding History

Figure 3 illustrates variation of the median levels of vWF Ag amongst the various blood groups in the study participants without bleeding history. The median Ag level of vWF of various blood groups were: blood group A Rh(D) positive [86.31 (55.97-107.18) IU/L], B Rh(D) positive [73.93 (43.03-168.98) IU/L], AB Rh(D) positive [81.52 (47.21-122.33) IU/L], O Rh(D) positive [57.35 (43.33- 74.19) IU/L] and O Rh(D) negative [65.05 (57.82-86.98) IU/L] with a p-value of 0.184.

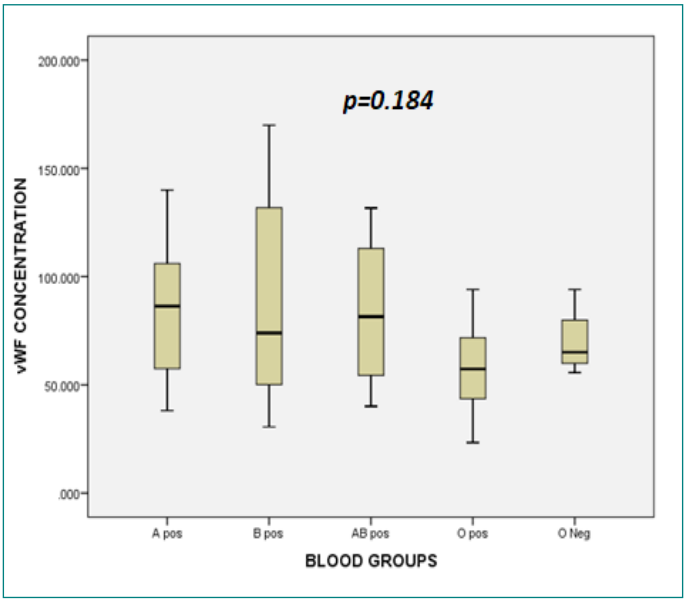

Figure 3. *Variation in Levels of vWF Ag and Blood Groups among Participants without Bleeding History. vWF= von Willebrand Factor, Ag. conc= Antigen concentration, IU/L= international units per litre. Data were compared using Kruskal Wallis H- Test was used. p-value=>0.05 was considered significant.*

3.6 Variations in the Levels of vWF Antigen among the Blood Groups of Study Participants with Abnormal Bleeding Tendencies.

Figure 4 illustrates variation of the median levels of vWF Ag among the various blood groups of the study participants with bleeding history. The median Ag levels of vWF are as follows: blood group A Rh (D) positive [4.99 (33.75-64.26) IU/L], B Rh (D) positive [84.94 (27.11-88.74) IU/L], AB Rh (D) positive [38.09 (23.93-53.61) IU/L] and blood group O Rh (D) positive [45.77 (30.74- 54.34) IU/L] with a p-value of 0.317. Blood group B Rh (D) positive however recorded the highest median Ag level of vWF.

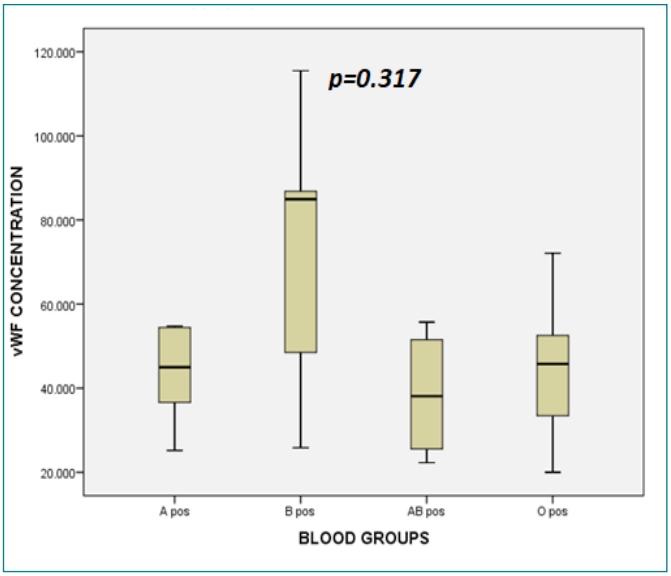

Figure 4. *Variation in Levels of vWF antigen among the Blood Groups of Study Participants with Abnormal Bleeding Tendencies. vWF= von Willebrand Factor, Ag. conc= Antigen concentration, IU/L= international units per litre. Data were compared using Kruskal Wallis H- Test was used. P<0.05 was considered insignificant.*

3.7 Association of vWF Levels with Contraceptive Usage in Participants with Abnormal Bleeding Tendencies

Figure 5 illustrates variation of the median levels of vWF antigen among the study participants with bleeding tendencies who take contraceptives and those that do not. The median antigen levels of vWF of those who take contraceptives and that of those who do not take contraceptives [57.28 (42.62-78.37) IU/L vs = 70.55 (41.50-91.53) IU/L, (p= 0.123)].

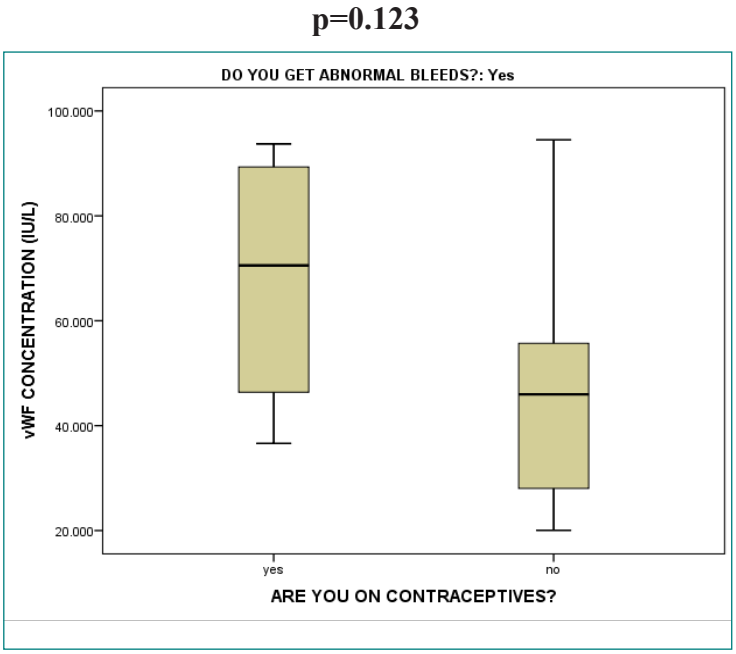

Figure 5. *Association of vWF levels with contraceptive usage in participants with abnormal bleeding history. vWF=von Willebrand Factor, Ag. conc= Antigen concentration, IU/L= international units per litre. Data were compared using Mann Whitney U- Test used. p-value=<0.05 was considered significant.*

3.8 Comparing Haemogram Parameters and vWF Antigen Levels among Blood Group O and Other Blood Groups

Table 4 shows comparison age, haemogram parameters and vWF Ag levels amongst participants with blood group O and those that are non-O blood group. Von Willebrand Factor antigen levels among the non-O blood groups were significantly higher than the O blood groups [62.2 (42.8-94.3) vs 52.5 (41.9-68.3),p=0.038]. All of the other associations yielded no statistical significance.

Table 4. *Haemogram Parameters and von Willebrand Factor Antigen Levels among the Study Participants in Relation to their Blood Groups.*

Variables	Blood groups		p-value
	O (n=46)	NON- O (n=44)	
vWF (IU/L)	52.5 (41.9-68.3)	62.2 (42.8-94.3)	**0.038**
AGE (YEARS)	21.50 (19.00-24.00)	20.00 (17.25-23.00)	0.105
TWBC x$10^9$$10^9$/L	2.7 (2.0-3.6)	2.7 (2.1-3.7)	0.771
LYM# x$10^9$$10^9$/L	1.4 (1.0-2.1)	1.4 (1.0-2.0)	0.744
MID# x$10^9$$10^9$/L	0.2±0.1	0.2±0.1	0.295
GRAN# x$10^9$$10^9$/L	1.1 (0.6-1.4)	1.1 (0.7-1.4)	0.844
RBC x$10^9$$10^9$/L	3.9±0.4	4.0±0.5	0.307
HGB (g/dL)	12.7±1.6	12.6±1.4	0.758
HCT%	34.8±3.5	34.3±3.7	0.546
RDW-CV (%)	14.6±1.3	15.2±1.4	0.051
MCV (fL)	90.0±8.8	87.9±8.9	0.242
MCH (pg)	30.4±3.7	32.2±1.7	0.281
MCHC (g/dL)	36.6±1.7	36.6±1.7	0.926
PLT (10^9/L)	306.4±118.2	307.8±111.3	0.953
PCT (%)	0.3±0.1	0.3±0.1	0.879
MPV (fL)	9.7±1.5	9.9±1.5	0.710
PDW (fL)	16.4±0.8	16.2±0.9	0.390
P-LCR	24.1±11.6	24.3±12.3	0.956

Table 4: n=Number of participants, TWBC=Total white blood cell count, LYM# =Absolute lymphocyte count, GRAN# = Absolute granulocyte count, MID# =Total of WBCs not categorised as LYM or GRAN, RBC=Total red blood cell count, HGB=Haemoglobin concentration, , HCT=Haematocrit, RDW-CV=Red blood cell distribution width-coefficient of variation, MCV=Mean cell volume, MCH=Mean cell haemoglobin, MCHC=Mean cell haemoglobin concentration, PLT= Platelet count, PCT= Plateletcrit, MPV=Mean platelet volume, PDW=Platelet distribution width. P-LCR= Platelet larger cell ratio. Parametric Data is shown in mean ± SD while non-parametric data is presented in Median (25th-75th percentile). The Independent T-Test was used to compare parametric data, and the Mann- Whitney U-Test was used to examine non-parametric data. P-values less than 0.05 were considered significant, whereas p-values more than 0.05 were judged non-significant.

4. Discussion

The magnitude of ABO's effect on plasma vWF antigen levels is noteworthy, given that ABO (H) glycan determinants differ only by a single terminal sugar moiety and are expressed on just a subset of vWF N- and O-linked glycans (Ward *et al*., 2020). Contrary to group A or group B members, group O members have a shorter half-life for VWF and 25–30% lower levels of both VWF and Factor VIII (Goel *et al*., 2021). This study assessed the association of ABO Rh typing and the levels of vWF in reproductive-aged women with bleeding tendencies.

Again, all participants were females in their reproductive ages, with the majority (73.3%) having their ages less than 20. The study subjects comprised of 30 females with a history of abnormal bleeding, and 60 females without any history of abnormal bleeding. Majority (56.7%) of the participants with abnormal bleeding history presented with abnormal gum bleeds, 20% presented with nose bleeds, 13,3% with vaginal bleeds, and 10% with both nose bleeds and gum bleeds. This is in contrast with the findings of Srivaths et al (2020) in a multicenter single arm observational cohort study in adolescents with low VWF–associated heavy menstrual bleeding (HMB) to describe the bleeding phenotype, HMB severity, and related complications. According to Srivaths and colleagues, 45% of subjects manifested cutaneous bleeds, 42% manifested epistaxis, 32% manifested oral cavity bleeds (Srivaths *et al*., 2020). It is not clear what might account for the observed trend in the current study. However, the majority bleeding through the gums it may be due to abrasion from toothbrushes while the subjects try to maintain oral hygiene. Those with vaginal bleeds had specifically, prolonged menstrual bleeds. It is worth noting that all participants with abnormal bleeding history bled through muco-cutaneous routes, which is in consonance with the bleeding routes in von Willebrand Disease, and also in congenital platelet disorders (Atiq *et al*., 2021). Among these participants with abnormal bleeding history, there were 13.3% of them on contraceptives. Those without history of abnormal bleeding were not on any contraceptives.

Furthermore, individuals with abnormal bleeding history had significantly increased plateletcrit (PCT),

mean platelet volume (MPV), and platelet large cell ratio (PLCR) as compared to those without abnormal bleeding history. The PCT is used to assess platelet production rate and/or platelet activation (Budak *et al*., 2016). Those with abnormal bleeding history also had significantly increased platelet count [p=0.114] and platelet distribution width PDW (fL) as compared to those without abnormal bleeding history. These differences however were not significant. Increased platelet activation is expected to present with reduced platelet count since the activated platelets would be consumed at a faster rate (Budak *et al*., 2016). These modifications call into question the platelet's functionality and may contribute to the aberrant bleeding seen in these patients. This raises a question on the functionality of the platelets in those with bleeding history. It also suggests that abnormal bleeding observed in these patients may not be due to only low levels of vWF, and that other bleeding defects such platelet function defects cannot be excluded. They can only be ruled out by performing other bleeding assessment tests.

The total WBC count [p= 0.004], absolute lymphocyte count [p= <0.001] and mean cell haemoglobin concentration MCHC [p=<0.001] for those with abnormal bleeding history were significantly higher than those without abnormal bleeding history. White blood cell count and lymphocyte count often increase in response to infection especially viral and fungal infections and in some cases, chronic bacterial infections (Jordan & Mitchell, 2015). The reason for the increased levels in patients with abnormal bleeding history is not known. It could however be due to compensation to the abnormal bleeding (Chaudhury *et al*., 2019).

The vWF levels of the entire study group was found to be 57.28 (42.66-83.84) U/L. In a 2022 study by Appiah et al (2022) in the Northern Ghana on healthy blood donors, with about 53.6% of them being males, the levels of vWF was found to be 111.45 (78.19–143.05) U/L (Appiah *et al.*, 2022). This vast difference in the levels of vWF may be due to the many differences that exist between the study subjects in both studies. For instance, the previous study had 36.9% of the study subjects being within the age brackets; 30-49 years whereas in the current study, the median age of the subjects without abnormal bleeds was 22years, with the oldest being 28 years. Again, the previous study had 59.5% of the subjects having non-O blood groups (which have been shown to have increased levels of vWF) as compared to 48.89% non-O blood groups in the current study. The levels of vWF in the apparently healthy subjects (those without abnormal bleeding history) in this current study was 65.98 (46.79-88.93) U/L. This is also lower when compared to the vWF levels in the apparently healthy females from the study by Appiah et al which was 91.64 (68.89–126.07) U/L. The age distribution, the ABO blood group distribution, and other factors may have contributed to this variation since they are known to influence the levels of vWF (Agrawal *et al*., 2023; Appiah *et al*., 2022; Tscharre *et al*., 2023).

Moreover, 51.11% (46) of all the study subjects were blood group O (both Rh(D) positive and negative) , and 7.8% of the subjects had blood group AB Rh(D) positive. Blood group A Rh(D) positive and B Rh(D) positive recorded equal representation (20%) in the study subjects. Similarly, Asuquo et al (2022), investigated the relationship between plasma Von Willebrand Factor Antigen levels, ABO and Rh (D) blood groups, and the risk of Sickle Cell Anaemia Vaso-Occlusive Syndrome, 61% of the total study population had blood group O, and 2% of subjects had blood group AB (Akpan & Asuquo, 2022). In another study by Appiah et al (2022), in the northern part of Ghana, 40.5% of the study subjects had blood group O and 6% had blood group AB (Appiah et al., 2022), agreeing with the findings of the current study. This may be due to the trend of the ABO blood group distribution in the general population (Doku *et al*., 2019; Doku *et al*., 2022).

The vWF levels in various blood groups followed the trend; O<AB<A<B. The results of this study agrees with the findings of Song et al from a prospective epidemiologic ARIC (Atherosclerosis Risk in Community) study of 11,673 subjects in the United States that found blood group B to have the highest vWF levels, and blood group O, the least (Song *et al*., 2015). The results however, contradicts their finding that blood group AB has higher vWF levels than blood group A. The results of this study disagrees with previous findings by (Appiah *et al*., 2022) within the same study area but on healthy blood donors, and (Akpan & Asuquo, 2022) in Nigeria, who suggest the trend; O<B<A<AB. It is worth noting that, the difference in the vWF levels among blood groups A, B, and AB was statistically not significant. The levels of vWF were also significantly higher in non-O blood group individuals than O blood group individuals in an observational cross sectional study on persons with non-severe Haemophilia A by Rejto et al (Rejtő *et al.*, 2020). Blood group O has been shown to have the least vWF level (Akpan & Asuquo, 2022; Appiah

et al., 2022; Song *et al*., 2015; Ward *et al*., 2020). This further buttresses the theory that the glycosylation pattern of the A and B blood group antigens influence the level of vWF as asserted by Ward et al (Ward *et al*., 2020).

The vWF levels in persons with abnormal bleeding history was significantly lower as compared to its levels in persons without abnormal bleeding history (p =0.002). This suggests that the abnormal bleeding may be due to the lower vWF levels. However, other bleeding assessment may be required in order to make a definitive diagnosis of von Willebrand Disease in these subjects. Participants with abnormal bleeding history who were on contraceptives had higher vWF levels than those who are not (p= 0.123) which was statistically not significant. However, studies conducted by Andersson et al (Andersson *et al*., 2012) found out that contraceptive usage increase vWF levels. It has also been suggested in many other studies (Hernandez-Juarez *et al*., 2015; Kluft *et al*., 2002; Rodriguez *et al*., 2020) that contraceptives influence the levels of vWF. Only four of the study subjects in this current study were on contraceptives. This relatively low number may have accounted for the differences in findings. The effects of these contraceptives on vWF are believed to be orchestrated through the hormones they contain, particularly oestrogen. Oestrogen has also been shown to be responsible for the hypercoagulability noted in pregnancy by increasing the levels of vWF and other coagulation factors (Castaman & James, 2019; Turan & Kadir, 2021).

5. Conclusion and Recommendation

Plasma vWF levels in the reproductive-aged women were influenced by their ABO blood group antigens. People with blood group O had the lowest levels of vWF. The difference in vWF levels between the A, B, and AB blood groups was insignificant. People with a history of abnormal bleeding had significantly lower amounts of vWF. Contraceptive users also reported considerably greater amounts of vWF.

Further studies should be done evaluating the antigenic dose of the A and B blood groups in relation to the levels of vWF. Also, studies on abnormal bleeding patients in which extensive bleeding assessment tests will be performed to ascertain other causes of these abnormal bleeds.

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Data Availability

All relevant data are available in this article and its supplementary file.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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