von Willebrand Disease in Hong Kong Chinese Women with Unexplained Menorrhagia

WK TAM MBBS, MRCOG
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Tuen Mun, Hong Kong
LK SIU MSc, MSc (Hons) Medical Laboratory Science
Department of Pathology, Tuen Mun Hospital, Tuen Mun, Hong Kong
YM LEUNG MBBS, MRCOG, FHKCOG
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Tuen Mun, Hong Kong
YT YEUNG BSc, AIMLS, MBA
Department of Pathology, Tuen Mun Hospital, Tuen Mun, Hong Kong
KM CHOW MBChB
CT TAM MBBS
WS WU MBChB
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Tuen Mun, Hong Kong
SF YIP FRCP, FRCPath
Department of Pathology, Tuen Mun Hospital, Tuen Mun, Hong Kong

Objectives: To study the prevalence of von Willebrand disease in Hong Kong Chinese women with menorrhagia and to evaluate the utility of 'Standard Bleeding Questionnaire' for the screening of menorrhagic women for von Willebrand disease.
Methods: Over an 8-month period, prospective data obtained from patients with unexplained menorrhagia recruited during their first gynaecology clinic visit were analysed. All of them were invited to fill in the 'Standard Bleeding Questionnaire' by themselves. In the final data analysis, there were 100 eligible patients.
Results: The prevalence of von Willebrand disease in the study population was 6% (type I, n=4; type II, n=2). The sensitivity of the individual questions in the questionnaire ranged from 0 to 100%. Combined analysis of three questions with the most satisfactory results (symptoms affecting daily life, symptoms since menarche, and a history of anaemia) yielded a sensitivity of 83%, specificity of 60%, positive predictive value of 12%, and negative predictive value of 98%.
Conclusion: The prevalence of von Willebrand disease in patients with unexplained menorrhagia was higher than that in the general population. Detailed history taking and use of simple screening questions can help identify this high-risk group for further diagnostic testing of von Willebrand disease.
Hong Kong J Gynaecol Obstet Midwifery 2013; 13(1):101-7

Keywords: Menorrhagia; Prevalence; Questionnaires; von Willebrand diseases

Introduction

Menorrhagia is a common clinical problem. Around 5 to 10% of women of reproductive age seek medical attention for menorrhagia. Uterine fibroids (30%) and polyps (10%) are the commonest causes. Less common causes include endometrial hyperplasia, cancer, or medical disease such as thyroid disorders. However, in more than 50% of subjects an anatomical pathology is not found in the genital tract, and menorrhagia remains unexplained[1].

In the past decade, there has been increasing awareness of haemostatic problems as the cause of unexplained menorrhagia in a significant number of patients. Menorrhagia is a common presenting symptom in women with bleeding disorders, of which von Willebrand disease (VWD) is the commonest inherited bleeding disorder and according to the literature in western populations, its quoted prevalence is reported to be approximately 1%[2,3]. The condition is due to a qualitative or quantitative deficiency of von Willebrand factor (VWF), which is important in the maintenance of primary haemostasis. There are three major types: type I is a partial quantitative deficiency of a normal VWF and accounts for 70 to 80% of all cases; type II (accounting for 20%) includes several qualitative defects

Correspondence to: Dr. SF Yip
Email: yipsf1@ha.org.hk

affecting its multimeric structure or function; and type III (5-10% of all cases) with complete deficiency of VWF and a secondary severe deficiency of FVIII[1,4,5]. The patients with VWD have a propensity for mucocutaneous bleeding, menorrhagia, easy bruising, epistasis, and postoperative wound bleeding[6-8].

The reported frequency of VWD in women with menorrhagia was 5 to 20%[9-14], which was substantially more than that in the general population. A systematic review estimated that the overall prevalence of VWD in women presenting with menorrhagia was 13%[15].

Most studies on the prevalence of VWD and bleeding disorders in women with menorrhagia were conducted in the West. There were only two studies in Asians—one from India and one from Taiwan, and both reported a prevalence rate of 16%[9]. Similar studies have not been conducted in the Hong Kong Chinese population.

The detection of haemostatic disorder in patients with menorrhagia demands a broad panel of specialised laboratory investigations. However screening all females with otherwise unexplained heavy menstrual flow for full haemostatic evaluation might not be economical from the public health perspective. In reality, many patients show normal investigation results, despite comprehensive testing if the disorder to be detected is not prevalent. Therefore, in the West, a cost-effective strategy to screen patients for haemostatic disorder was proposed. In 2008, the American College of Obstetricians and Gynecologists (ACOG) advocated the use of a simple questionnaire-based tool to screen females before more elaborate evaluation for bleeding disorders[16,17]. Screening was considered positive if any one of the following four criteria were met: (1) duration of menses of >7 days and the women reported either flooding or impairment of daily activities with most periods; (2) a history of treatment for anaemia; (3) a family history of a diagnosed bleeding disorder; (4) a history of excessive bleeding with tooth extraction, delivery, miscarriage, or surgery. A combination of eight questions in these four categories demonstrated a high sensitivity of up to 82%[17]. This questionnaire may be a simple and useful tool to aid practising gynaecologists in Hong Kong for the diagnostic evaluation of patients with menorrhagia.

The purpose of our study was to investigate the prevalence of bleeding disorder and notably VWD in women with menorrhagia in Hong Kong. We set out to study the clinical characteristics of these patients and validate this 'Standard Bleeding Questionnaire' (SBQ) for selecting patients warranting more comprehensive diagnostic testing.

Methods

Study Subjects

A prospective observational cohort study was recruited from March to December 2011. All the patients were Chinese, aged 18 to 55 years, attending the gynaecological outpatient clinic, Tuen Mun Hospital, Hong Kong. They all had established menorrhagia, based on fulfilling any one of the following criteria[4,15,18-20]—(1) menses duration of >7 days; (2) heavy flow of >4 days; (3) requirement of pad change in less than 2 hours during a heavy flow period; (4) soaking through bed clothes; and (5) anaemia with a haemoglobin level of <116 g/l.

Patients were excluded from the study if they had menorrhagia: (1) due to uterine pathology noted from physical examination, endometrial aspiration, or pelvic ultrasound (e.g. fibroids, endometrial polyp, endometrial hyperplasia, and endometrial cancer); (2) due to any medical (non-haematological) disease such as hypothyroidism or hyperthyroidism; (3) associated with use of anticoagulants within the past 2 months; (4) associated with use of an intrauterine device; and (5) associated with use of an antiplatelet agent (non-steroidal anti-inflammatory drug, aspirin, or clopidogrel) within the last 14 days.

Consent was obtained from all patients and the study was approved by the hospital institutional review board.

Clinical Assessment

Eligible patients were invited to fill in the SBQ (Appendix) by themselves. This questionnaire was a Chinese translation modified from a screening questionnaire published by ACOG in 2008, and included questions also suggested by the National Heart, Lung, and Blood Institute 2008 Guidelines[16,17].

A routine gynaecological history was obtained and an examination (abdominal and per-vaginal examination) performed by qualified gynaecologists. Pelvic ultrasound was performed for patients suspected of having a uterine pathology. An endometrial aspirate was obtained for all women aged >40 years, or with other risk factors (according to routine institutional practice).

Questionnaire

The questionnaire with 16 questions was given to all study participants. The questions assessed the severity of menstrual bleeding, family history of bleeding disorder,

excessive bleeding after specific events (tooth extraction, surgery, or delivery), and a history of anaemia as well as its response to any treatment. Each question required an answer with a pre-coded response; either 'yes', 'no', or 'unknown'. The questionnaire also included several 'contingency questions', for which a 'yes' response elicited further questions. If the answer was 'no', such subsequent questions were skipped. All the 'unknown' answers were treated as not having that problem.

Laboratory Assessment

For all patients, 10 ml of blood was collected for haemostatic studies (complete blood count, prothrombin time [PT] and activated partial thromboplastin time [APTT], fibrinogen, Factor VIII, VWF:Ag, VWF:ristocetin cofactor [RCof] activity). Thyroid function tests were also checked for symptomatic patients. The measurement of RCof activity for VWF was measured by a commercial assay kit (model 700 Aggregometer; Chrono-Log Corporation, USA). VWF antigen assay was measured using a VIDAS VWF kit (Bimerieux Corp, France). Factor VIII assay was measured by a one-stage APTT assay in a Sysmex CA-7000 Coagulometer (Siemens, Germany).

All patients diagnosed to have VWF abnormalities or VWD were required to have the consistent abnormalities demonstrated in repeat samples. Type I VWD was diagnosed if both VWF:Ag and VWF:RCof were concordantly reduced below the reference range. The diagnosis of type II VWD was established when VWF:RCof level was reduced and the VWF:RCof / VWF:Ag ratio of ≤0.6. Type II VWD abnormality was suggested when the VWF:RCof level was borderline and still within the normal reference range, but the VWF:RCof / VWF:Ag ratio was consistently reduced to ≤0.6.

Results

A total of 108 Chinese women were recruited from the outpatient clinic. Two of these were excluded as they had uterine fibroids (subsequently confirmed by ultrasound), three because endometrial sampling showed abnormal uterine pathology (polyp, complex hyperplasia and carcinoma of corpus), and three others as they defaulted blood taking. The remaining 100 patients who satisfied the entry criteria completed the bleeding questionnaire and had blood testing were included in the analysis.

Patient Characteristics

The mean age of the patients was 43.7 (range, 19-55) years, their mean haemoglobin level was 114.2 (range, 72-146) g/l. All the patients had normal platelet counts, fibrinogen levels, PTs, and APTTs. The laboratory characteristics of all patients are summarised in Table 1.

Identification of Patients with Reduced von Willebrand Factor and von Willebrand Disease

Six of the 100 patients were confirmed to have consistently abnormal VWF level parameters after repeat testing and diagnosed VWD. Thus, the prevalence of VWD in this study was 6%. Four of these patients manifested type I abnormalities concordant with reduced VWF:RCof and VWF:Ag levels, whereas two patients manifested VWD type II abnormalities with a more significant relative reduction of VWF:RCof than VWF:Ag. The haemostatic results of these six patients are shown in Table 2. In all, four of these six patients (3 type I, 1 type II) had mild anaemia.

Table 1. Clinical and laboratory characteristics of VWD and non-VWD patients

Characteristic	Mean ± standard deviation			p Value
	All patients (n=100)	No bleeding disorders (n=94)	VWD (n=6)	
Age (years)	43.7 ± 7.2	46.2 ± 4.1	43.6 ± 7.31	0.40
Haemoglobin (g/l)	114.2 ± 16.9	114.4 ± 16.9	112.2 ± 16.5	0.76
Platelet (g/l)	282.5 ± 74.2	283.8 ± 75.4	262.7 ± 50.8	0.50
PT	10.9 ± 0.5	10.9 ± 0.6	10.9 ± 0.4	0.87
APTT	28.7 ± 2.0	28.5 ± 1.9	31.4 ± 1.5	0.004
Fibrinogen (g/l)	2.8 ± 0.6	2.8 ± 0.6	2.7 ± 0.6	0.71
VWF:Ag (%)	98.3 ± 25.6	96.8 ± 31.9	53.3 ± 6.2	0.13
VWF:RCof (%)	94.2 ± 32.7	100.0 ± 24.1	72.5 ± 36.6	0.001
Factor VIII (%)	140.1 ± 47.7	143.0 ± 47.7	94.7 ± 45.7	0.127

Abbreviations: APTT = activated partial thromboplastin time; PT = prothrombin time; VWD = von Willebrand disease; VWF:Ag = von Willebrand factor antigen; VWF:RCof = von Willebrand factor: ristocetin cofactor activity

Results Based on Standard Bleeding Questionnaire

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of individual questions are shown in Table 3. The sensitivity of the questions ranged from 0 to 100%. As a group, patients with VWD showed more frequent menorrhagia since menarche and an anaemia history than those without VWF abnormalities. In all, 67% (4/6) of the patients with VWD had menorrhagia since menarche compared with 35% (33/94) in those without the disease. Similar results were evident for a history of anaemia; with 67% (4/6) in patients with VWD compared with 40% (38/94) in those without the disease. Family history and personal bleeding history (bruising, epistaxis, gastrointestinal, and dental bleeding) did not differ significantly between the groups with and without VWD. Two patients with VWF abnormalities had

Table 2. The data of haemostatic tests of the six patients with VWD

Patient No.	Age (years)	VWF:Ag (%)	VWF:RCof (%)	Factor VIII (%)	Haemoglobin (g/l)	VWF:Ag/ VWF:RCof	Type of VWD
Reference range	-	52-200	58-166	50-150	116-155	-	-
12	45	134	60	182	106	0.4	II
49	49	50	52	63.4	90	1	I
61	47	54	50	64.4	115	0.9	I
75	39	50	47	96	99	0.9	I
90	51	103	62	98	130	0.6	II
98	46	46	49	68.2	133	1.1	I

Abbreviations: VWD = von Willebrand disease; VWF:Ag = von Willebrand factor antigen; VWF:RCof = von Willebrand factor: ristocetin cofactor activity

Table 3. Statistical characteristics of individual questions in the questionnaire

Question No.	Question	% positive (positive/ total)	% (95% CI)			
			Sensitivity	Specificity	PPV	NPV
1	Menses >7 days	74 (74/100)	67 (24-94)	26 (17-36)	5.4 (1.7-14)	92 (73-99)
2	Flooding sensation	90 (90/100)	100 (52-100)	10.6 (5-19)	6.7 (2.7-14)	100 (66-100)
3	Symptoms affect daily life	60 (60/100)	50 (14-86)	39.4 (30-50)	5 (1.3-15)	92.5 (79-98)
4	Symptoms since menarche	37 (37/100)	67 (24-94)	65 (54-74)	10.8 (4-26)	96.8 (88-99)
5	History of anaemia	42 (42/100)	67 (24-94)	59.6 (49-69)	9.5 (3-24)	97 (76-97)
6	Positive family history	2 (2/100)	0 (0-4.8)	98 (92-100)	0 (0-8)	94 (87-97)
7	Dental surgery (n=55)					
7.1	Bleeding after dental surgery	3.6 (2/55)	0 (0-8)	96 (86-99)	0 (0-8)	96 (86-99)
8	General surgery (n=37)					
8.1	Excessive bleeding after general surgery	2.7 (1/37)	50 (27-97)	100 (88-100)	100 (5-100)	97 (84-100)
9	Pregnancy (n=82)					
9.1	Excessive bleeding after delivery/abortion	3.7 (3/82)	0 (0-5)	96 (88-99)	0 (0-7)	94 (85-98)
10	Epistaxis	4 (4/100)	0 (0-5)	96 (89-99)	0 (0-6)	94 (86-97)
11	Bruises >2 cm	9 (9/100)	0 (0-5)	90 (8-95)	0 (0-4)	93 (86-97)
12	Small wound bleeding >5 mins	4 (4/100)	0 (0-5)	96 (89-99)	0 (0-6)	94 (86-97)
13	Oral/GI bleeding	4 (4/100)	0 (0-5)	96 (89-99)	0 (0-6)	93.8 (86-97)
14	History of transfusion	8 (8/100)	0 (0-5)	92 (83-96)	0 (0-4)	94 (86-97)
15	History of haemorrhagic cyst	4 (4/100)	0 (0-5)	96 (89-99)	0 (0-6)	94 (86-97)
16	Failed treatment	18 (18/100)	0 (0-5)	81 (71-88)	0 (0-2.2)	93 (84-97)

Abbreviations: CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; GI = gastrointestinal

Table 4. Statistical results in combined assessment with questions 3-5

No. of positive questions (Question 3, 4, and 5)	% (95% CI)			
	Sensitivity	Specificity	PPV	NPV
≥1	83 (36-99)	13 (7-22)	6 (2-14)	92 (6-99)
≥2	83 (36-99)	60 (49-69)	12 (4-26)	98 (89-99)
≥3	17 (9-64)	92 (83-96)	11 (1-49)	95 (87-98)

Abbreviations: CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value

undergone prior surgery, one of whom endured excessive bleeding. Whereas none of the 36 patients without VWF abnormalities who had surgery suffered excessive bleeding.

In view of the wide ranges of sensitivity and specificity for individual questions, we specifically studied the three questions that demonstrated the highest values (Questions 3, 4, and 5). Scoring was assigned based on the number of questions that yielded a positive answer. One point was assigned for each question. Question 8.1 (about excessive bleeding after general surgery) was not included in the analysis, because of the low answer rate (only 2 VWD patients had been challenged), even though that question yielded a high sensitivity (50%) and specificity (100%), and the PPV and NPV rates were 100% and 97%, respectively. The optimal cutoff point for this 3-question scoring system was ≥2 (sensitivity of 83% and specificity of 60%; Table 4).

Discussion

Menorrhagia is one of the commonest reasons for referral to the gynaecology outpatient clinic. However, most obstetricians and gynaecologists may not be familiar with the inherited bleeding disorders that give rise to menorrhagia[21].

Among these, VWD is the commonest in the western populations, and can account for up to one-fourth of the cases of unexplained menorrhagia. However, it is an under-diagnosed disease in most parts of the world, which could be because of the relatively mild bleeding symptoms in most affected patients, lack of awareness, and the complexity of the laboratory tests involved and their interpretation. In managing patients with menorrhagia, any gynaecological treatment that reduces heavy menstrual bleeding may be appropriate, depending on the woman's age, gynaecological conditions, and reproductive plans. Medical treatment such as tranexamic acid and oral contraceptive pills remained the first-line treatment. Surgical intervention is sometimes required in patients who cannot tolerate or are unresponsive to medical treatment. Patients with bleeding disorders or VWD deserve special attention and precautions, including the use of desmopressin (1-desamino-8-D-arginine vasopressin), replacement of deficient factors, family studies, and counselling. Moreover, for patients with platelet function disorders plus VWD, use of non-steroidal anti-inflammatory drugs is discouraged[1,22,23].

In addition to menorrhagia, women with VWD are reported to have higher risk of haemorrhagic ovarian cysts and postpartum haemorrhage. Surgical therapy, tranexamic acid, and factor replacement have been used acutely to manage haemorrhagic ovarian cysts[8].

In the present study, the prevalence of the VWF abnormalities and VWD in Chinese women with unexplained menorrhagia was 6%. Thus, our VWD prevalence rate was at the lower end of the spectrum cited in the international literature[9-14,24].

Study design and its context, and the referral dynamic of the patients can have significant influence on estimations of prevalence. Some of the published studies included patients with menorrhagia due to organic causes (e.g. fibroids)[9-12], whereas ours excluded such patients. Our study recruited patients from a general gynaecology outpatient clinic with patients mainly referred by family physicians. We did not recruit inpatients who might have presented late (with more severe symptoms). Moreover, some younger patients were followed up by the paediatricians, not gynaecologists. Some published studies, however, involved patients recruited from more specialised centres or from coagulation clinics[9,10,12]. Therefore, aside from ethnic differences, the setting of the studies and hence recruitment bias might have accounted for higher prevalence rates reported in some of the studies. The Taiwan study was conducted in a coagulation clinic and observed a VWD rate as high as 16%[9]. Our study in Asian Chinese appears to be the first study of the genuine prevalence of VWD in general population with menorrhagia.

Our study relied on the patient's own subjective recall and assessment of the menorrhagia rather than

any objective tools. The pictorial blood loss assessment chart and direct measurement by alkaline haematin are the recommended tools to aid the objective documentation of the blood loss in patients with menorrhagia[20]. In the ACOG study, the pictorial chart enhanced the sensitivity and specificity of the SBQ with respect to identification of VWD. However, these tools are not convenient for patients or easy to be implemented in our local population. Many women in our locality refuse to undertake such measurements. Although our study can be criticised as imprecise, as we relied on memory recall, it more accurately reflects real-life practice and allows better integration of the findings with the everyday management of patients having menorrhagia.

Due to the complexity and cost of the diagnostic assays, an efficient screening tool can help to identify those at high risk who warrant testing[25]. An American group suggested using a screening tool with eight questions in four categories to identify such patients[17]. In the current study, 16 questions covering menstrual symptoms, family history, other bleeding, and response to treatment were asked about. The sensitivity of individual questions ranged from 0 to 100%. However unlike the former study, questions concerning the family history of bleeding disorder and personal history of bleeding showed a relatively poor sensitivity, with most of the questions scoring 0% sensitivity. Only Question 8.1 enquired into bleeding after general surgery had a sensitivity of 50%. Of note are the two VWD patients who had prior general surgery, one of whom reported excessive bleeding, whereas none of the 35 recipients of surgery patients (not having VWF) reported such complaints. Although the response rate to this question was too low to judge its predictive power, it can be inferred that most patients with genuine VWD have mild symptom whenever the haemostatic challenge is not severe enough. A positive personal and family history of bleeding is helpful, but not necessarily present. Penetrance of type I VWD is not complete and there are influences from other genes including ABO blood group, and acquired factors that modulate the phenotype. Our observation of VWD prevalence is nevertheless in agreement with reports and diagnostic recommendations from international guidelines[1]. Moreover, we realise that not all women are fully aware of their past health and the health status of their family members. The positive results retrieved from questions about bleeding could be an underestimate.

Nevertheless our study identified for the first time a clinical tool that may aid the identification of high-risk patients for further haemostatic investigation. Using a three-question scoring system, and scoring a total of ≥2 for questions: (1) long history of menorrhagia since menarche, (2) a history of anaemia, (3) severe symptoms that affect their daily life, had a sensitivity of 83% and specificity of 60%; with a PPV of 12% and NPV 98% for VWD. Our study was limited by the small study population and the low prevalence of VWD. This was also a single-institution study. The validity of the bleeding questionnaire and the three-question scoring system remain to be proven in future multicentre studies.

In conclusion, menorrhagia is one of the commonest gynaecological complaints. Our study demonstrated that VWD accounted for 6% of women with unexplained menorrhagia, which was higher than that in the general population that is quoted as 1% worldwide. Further testing of VWD disease should be considered in patients with prolonged history of unexplained menorrhagia and those with severe symptoms and anaemia. Failure to identify patients with VWD will limit medical therapeutic options such as desmopressin and increase the risk of haemorrhagic complication associating with surgical interventions[26-28].

Acknowledgement

The author would like to thank Miss Wendy Yau for the advice and statistical support on the preparation of this manuscript.

Appendix

Additional material related to this article can be found on the HKJGOM website. Please go to <http://www.hkjgom.org>, search for the appropriate article, and click on Full Text (PDF).

References

1. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia* 2008; 14:171-232.
2. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987; 69:454-9.
3. Werner EJ, Broxson EH, Tucker EL, et al. Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr* 1993; 123:893-8.
4. Kouides PA, Kadir RA. Menorrhagia associated with laboratory

abnormalities of hemostasis: epidemiological, diagnostic and therapeutic aspects. *J Thromb Haemost* 2007; 5 Suppl 1:175-82.
5. Favaloro EJ, Koutts J. Laboratory assays for von Willebrand factor: relative contribution to the diagnosis of von Willebrand's disease. *Pathology* 1997; 29:385-91.
6. Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. *J Thromb Haemost* 2005; 3:2619-26.
7. Tosetto A, Rodeghiero F, Castaman G. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). *J Thromb Haemost* 2006; 4:766-73.
8. Sadler JE, Mannucci PM, Berntorp E. Impact, diagnosis and treatment of von Willebrand disease. *Thromb Haemost* 2000; 84:160-74.
9. Chen YC, Chao TY, Cheng SN, et al. Prevalence of von Willebrand disease in women with iron deficiency anaemia and menorrhagia in Taiwan. *Haemophilia* 2008; 14:768-74.
10. Dilley A, Drews C, Miller C, et al. von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. *Obstet Gynecol* 2001; 97:630-6.
11. Edlund M, Blombäck M, von Schoultz B, et al. On the value of menorrhagia as a predictor for coagulation disorders. *Am J Hematol* 1996; 53:234-8.
12. Goodman-Gruen D, Hollenbach K. The prevalence of von Willebrand disease in women with abnormal uterine bleeding. *J Womens Health Gend Based Med* 2001; 10:677-80.
13. Philipp CS, Dilley A, Miller CH, et al. Platelet functional defects in women with unexplained menorrhagia. *J Thromb Haemost* 2003; 1:477-84.
14. Woo YL, White B, Corbally R, et al. von Willebrand's disease: an important cause of dysfunctional uterine bleeding. *Blood Coagul Fibrinolysis* 2002; 13:89-93.
15. Shankar M, Lee CA, Sabin CA, et al. von Willebrand disease in women with menorrhagia: a systematic review. *BJOG* 2004; 111:734-40.
16. James AH, Manco-Johnson MJ, Yawn BP, et al. Von Willebrand disease: key points from the 2008 National Heart, Lung, and Blood Institute guidelines. *Obstet Gynecol* 2009; 114:674-8.
17. Philipp CS, Faiz A, Dowling NF, et al. Development of a screening tool for identifying women with menorrhagia for hemostatic evaluation. *Am J Obstet Gynecol* 2008; 198:163.e1-8.
18. James AH. Women and bleeding disorders. *Haemophilia* 2010; 16 Suppl 5:S160-7.
19. James A, Matchar DB, Myers ER. Testing for von Willebrand disease in women with menorrhagia: a systematic review. *Obstet Gynecol* 2004; 104:381-8.
20. ACOG Committee on Practice Bulletins—Gynecology. American College of Obstetricians and Gynecologists. ACOG practice bulletin: management of anovulatory bleeding. *Int J Gynaecol Obstet* 2001; 72:263-71.
21. Chi C, Shiltagh N, Kingman CE, et al. Identification and management of women with inherited bleeding disorders: a survey of obstetricians and gynaecologists in the United Kingdom. *Haemophilia* 2006; 12:405-12.
22. Siegel JE, Kouides PA. Menorrhagia from a haematologist's point of view. Part II: management. *Haemophilia* 2002; 8:339-47.
23. James AH, Kouides PA, Abdul-Kadir R, et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol* 2009; 201:12 e1-8.
24. Kouides PA. Bleeding symptom assessment and hemostasis evaluation of menorrhagia. *Curr Opin Hematol* 2008; 15:465-72.
25. Böhm M, Täschner S, Kretzschmar E, et al. Cold storage of citrated whole blood induces drastic time-dependent losses in factor VIII and von Willebrand factor: potential for misdiagnosis of haemophilia and von Willebrand disease. *Blood Coagul Fibrinolysis* 2006; 17:39-45.
26. American College of Obstetricians and Gynecologists Committee on Adolescent Health Care; American College of Obstetricians and Gynecologists Committee Gynecologic Practice. ACOG Committee Opinion No. 451: Von Willebrand disease in women. *Obstet Gynecol* 2009; 114:1439-43.
27. Ahuja SP, Hertweck SP. Overview of bleeding disorders in adolescent females with menorrhagia. *J Pediatr Adolesc Gynecol* 2010; 23(6 Suppl):S15-21.
28. Kujovich JL. von Willebrand's disease and menorrhagia: prevalence, diagnosis, and management. *Am J Hematol* 2005; 79:220-8.

Appendix. Standard Bleeding Questionnaire 出血性疾病問卷調查

請回答以下全部問題 Please answer all questions (Q)		請圈出適當的答案 Please circle where appropriate			職員專用 Official Use
「病人」請自行回答第1至16題 Patient to answer Q1 to Q14 by yourself					
1.	你的月經一般持續7天或以上 （從開始直至出血完全停止） Your menstrual flow last ≥7 days (from start of menstruation to complete cessation)	是 Yes	否 No	不清楚 Don't Know	1
2.	月經期間你常有溢流或湧血的感覺 You experience "flooding" or "gushing" sensation during every or most periods	是 Yes	否 No	不清楚 Don't Know	1
3.	月經限制你的日常活動，如工作、家務、運動或社交活動 Every period or most periods limit your daily activities such as work, housework, exercise, or social activities	是 Yes	否 No	不清楚 Don't Know	1
4.	由少女初次到現在，出血量都普遍為多 Menorrhagia since menarche	是 Yes	否 No	不清楚 Don't Know	2
5.	你有治療貧血的紀錄 Have you ever been treated for anaemia?	是 Yes	否 No	不清楚 Don't Know	1
6.	你的家人被診斷出患有出血性疾病 Has anyone in your family ever been diagnosed with a bleeding disorder?	是 Yes	否 No	不清楚 Don't Know	1, 2
7.	你曾經接受拔牙或牙科手術 Have you ever had a tooth extracted or had dental surgery before?	是 Yes	否（跳至Q8） No (Go to Q8)	不清楚 Don't Know	
7.1.	拔牙後或牙科手術後，有止血困難的問題 Did you have problem with bleeding after tooth extraction or dental surgery?	是 Yes	否 No	不清楚 Don't Know	1, 2
8.	你曾經進行牙科以外的手術 Have you ever had surgery other than dental surgery?	是 Yes	否（跳至Q9） No (Go to Q9)	不清楚 Don't Know	
8.1.	手術後有止血困難的問題 Did you have bleeding problem with surgery?	是 Yes	否 No	不清楚 Don't Know	1, 2
9.	你曾經懷孕 Have you ever had surgery other than dental surgery?	是 Yes	否（跳至Q10） No (Go to Q10)	不清楚 Don't Know	
9.1.	分娩或流產後，有止血困難的問題 Have you ever had bleeding problem following delivery or after a miscarriage?	是 Yes	否 No	不清楚 Don't Know	1, 2
10.	過去一年，曾試過鼻出血，流血情況一般會超過10分鐘並要包紮治療 Did you have epistaxis, generally bilateral, >10 minutes duration, once in the last year, possibly necessitating packing or cautery?	是 Yes	否 No	不清楚 Don't Know	2
11.	在沒有受傷的情況下，身上有超過2厘米直徑的明顯瘀傷 Did you have notable bruising >2 cm in diameter without injury?	是 Yes	否 No	不清楚 Don't Know	2
12.	就算是小傷口或細微的切傷，仍會持續出血超過5分鐘 Did you have excessive bleeding lasting >5 minutes resulting from minor wound bleeding or trivial cut?	是 Yes	否 No	不清楚 Don't Know	2
13.	在口腔/腸胃沒有明顯受傷的情況下，也曾出現流血的問題 Did you have bleeding problem of the oral cavity or gastrointestinal tract without an obvious anatomic lesion?	是 Yes	否 No	不清楚 Don't Know	2
14.	曾因出血過多而要接受輸血 Did you have haemorrhage that required blood transfusion?	是 Yes	否 No	不清楚 Don't Know	2
15.	於排卵期間，曾出現卵巢囊腫/黃體囊腫出血並可能產生痛楚 Did you have haemorrhage from ovarian cysts or corpus luteum, possibly with accompanying pain during ovulation?	是 Yes	否 No	不清楚 Don't Know	2
16.	經血過多的情況，雖曾接受一般的治療，但效果未如理想 Did the menorrhagia fail to respond to conventional management before?	是 Yes	否 No	不清楚 Don't Know	2
Thank you 多謝您的寶貴意見					