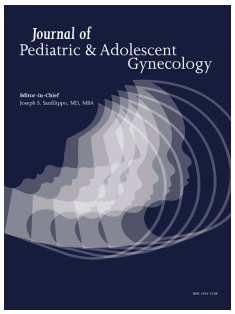
Accepted Manuscript



Bleeding disorders in Adolescents with Heavy Menstrual Bleeding (HMB): The Queensland Statewide Paediatric and Adolescent Gynaecology Service

O'Brien B, Mason JA, Kimble RMN

PII: S1083-3188(18)30356-5

DOI: https://doi.org/10.1016/j.jpag.2018.11.005

Reference: PEDADO 2299

To appear in: *Journal of Pediatric and Adolescent Gynecology*

Received Date: 28 August 2018

Revised Date: 9 November 2018

Accepted Date: 12 November 2018

Please cite this article as: B O'B, JA M, RMN K, Bleeding disorders in Adolescents with Heavy Menstrual Bleeding (HMB): The Queensland Statewide Paediatric and Adolescent Gynaecology Service, *Journal of Pediatric and Adolescent Gynecology* (2018), doi: https://doi.org/10.1016/j.jpag.2018.11.005.

Bleeding disorders in Adolescents with Heavy Menstrual Bleeding (HMB): The Queensland Statewide Paediatric and Adolescent Gynaecology Service.

O'Brien B [1,2], Mason JA [3], Kimble RMN [1,2].

1. Statewide Paediatric and Adolescent Gynaecology Service, Royal Brisbane and Women's Hospital and Lady Cilento Children's Hospital, Brisbane, Queensland, Australia
2. University of Queensland, Faculty of Medicine, Brisbane, Queensland, Australia
3. Queensland Haemophilia Centre, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

Corresponding Author: Dr Brooke O'Brien

Email: drbrookeob@gmail.com

Word Count: 3802

Abstract

Study Objective: Heavy menstrual bleeding (HMB) is a common gynaecological complaint among young females with up to 40% having experienced HMB. Bleeding disorders are increasingly being recognised in adolescents and young adults with HMB. The aim of this study was to determine the prevalence of bleeding disorders in adolescents with HMB, among patients presenting to the Queensland Statewide Paediatric and Adolescent Gynaecology (PAG) Service between July 2007 to July 2017.

Design, Settings, Participants, Interventions, and Main Outcome Measures: The study was a retrospective review of 124 adolescent females aged 8 to 18 years with HMB presenting to the Queensland PAG Service, Brisbane, Australia. The primary outcome measure was diagnosis of a bleeding disorder, with secondary outcomes including iron deficiency and/or anaemia and treatment modalities.

Results: Screening for bleeding disorders was performed in 62.1% (77/124) of patients with HMB. Twenty-seven adolescents were diagnosed with a bleeding disorder, giving a prevalence of 21.7% (27/124) in those with HMB, and 35% (27/77) with HMB that were screened. Of these 35%, von Willebrand Disease (VWD) was the most common bleeding disorder, found in 51.6% (14/27), followed by inherited platelet function disorders diagnosed in 33.3% (9/27), thrombocytopenia (inherited or acquired) in 11.1% (3/27), and Factor IX deficiency in 3.7% (1/27). Iron deficiency and/or anaemia was diagnosed in 49.5% (53/107) of patients with HMB that were screened for this, and 70.3% (19/27) of those diagnosed with a bleeding disorder.

Conclusion: Adolescents with HMB presenting to a tertiary PAG service should be screened for bleeding disorders, given the considerably high prevalence in this at-risk population.

Key words: Heavy Menstrual Bleeding, Adolescents, Bleeding disorders, Paediatric Adolescent Gynaecology, von Willebrand's Disease.

Introduction

Heavy menstrual bleeding (HMB) is a common gynaecological complaint among adolescents with up to 40% having experienced HMB. [1] In many cases, immaturity of the hypothalamic-pituitary-ovarian axis, leading to anovulatory cycles, is thought to be the underlying cause for heavy menses. However, in young women with HMB, particularly in those who are presenting with anaemia and those who are not responding to the usual hormonal attempts to manage HMB, it is prudent to consider the presence of an underlying bleeding disorder.

Bleeding disorders are increasingly being recognised in women with HMB, and several studies have shown that 10 – 62% of adolescents with HMB have an underlying bleeding disorder. [2, 3, 4] These studies show the prevalence of Von Willebrand's Disease (VWD) to be 5 - 36%, platelet function disorders (PFD) to be 2 - 44%, thrombocytopenia to be 13-20%, and clotting factor deficiencies to be 8-9%. [5,6]

The aim of this study was to determine the prevalence of bleeding disorders in adolescents with HMB presenting to a tertiary hospital Paediatric and Adolescent Gynaecology (PAG) service.

Methods

This study was a retrospective review of all patients with HMB that presented to the Queensland Paediatric and Adolescent Gynaecology (PAG) Service from July 2007 to July 2017. Ethics approval was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/17/QRBW/488). All patients coded on our database presenting with menstrual disorders were identified, and the medical records of those with HMB were reviewed. Data was collected on patient demographics, clinical history and symptoms, pathology results, therapeutic regimens, outcomes and follow up. SPSS version 22 (IMB Corp) was used for all analysis.

Clinical and laboratory findings from patients with bleeding disorders were independently reviewed by a Specialist Paediatric Haematologist to ensure that patients were classified in accordance with recognised International criteria. The difficulty in accurately diagnosing mild Type 1 VWD has been well described, presenting classification challenges in both the clinical and research spheres. [6, 7] For the purposes of this study, and in keeping with recent British guidelines, Type 1 VWD was classified as a positive bleeding and/or family history with reduced VWF:Ag and VWF:RCo, where either VWF:Ag or VWF:RCo was <0.3 U mL^{-1} with a Rco:Ag ratio of >0.6. "Low VWF" was classified as a positive bleeding history and/or family history with VWF:Ag and VWF:RCo levels of 0.30–0.49 U mL^{-1}. Criteria for classification of subtypes of type 2 VWD and type 3 VWD were in keeping with recent published guidelines. [9] Platelet function disorders were classified by the Haematologist in keeping with recognised diagnostic criteria according to blood film findings, platelet aggregation studies (light transmission aggregometry) and platelet electron microscopy findings. [10] Dense body (granule) deficiency was specifically defined as a dense granule

count of 2.5 or less by electron microscopy [10], replicated on two occasions (according to locally established protocols). Where there was a clearly abnormal bleeding history and abnormally prolonged automated platelet function testing (PFA-100) without other cause, but definitive platelet function testing had not been performed, the temporary designation was "possible platelet function disorder". Haemophilia A or B was classified according to factor VIII or factor IX levels of < 1 – 40% respectively, with severe < 1%, moderate 1 – 5% and mild 5 – 40%. Known carriers of Haemophilia A or B who had a factor VIII or IX level of 40 - 60% respectively, and a bleeding history, were designated as symptomatic carriers of Haemophilia A or B. [11]

Results

One hundred and twenty-four (124) adolescents presented with HMB from a total cohort of 635 adolescents referred to the PAG service over the study time for a multitude of gynaecological conditions **(Figure 1).** The median age of adolescents with HMB was 14 years and 3 months (range 10 years and 9 months to 18 years and 5 months). Screening for bleeding disorders was performed in 62.1% (77/124) of all patients presenting with HMB. Overall, 21.7% (27/124) of all patients with HMB, and 35% (27/77) of those screened had a bleeding disorder. VWD was the most common bleeding disorder and diagnosed in 51.6% (14/27) **[Figure 2].** Of these, 6 adolescents were classified as low VWF and 8 adolescents were classified as Type 1 VWD. There were no patients in this study with rarer, more severe forms of VWD, such as type 2 or type 3 VWD. Platelet function disorders were detected (or strongly suspected) in 33.3% (9/27), of which dense body deficiency was the most common form confirmed, found in 4 adolescents. Thrombocytopenia was diagnosed in

11.1% (3/27), of which 2 were acquired (immune thrombocytopenia) and 1 were inherited. Factor IX deficiency (Symptomatic carrier of Haemophilia B) was diagnosed in 3.7% (1/27).

Iron deficiency and/or anaemia was screened for in 86.3% (107/124) and diagnosed in 49.5% (53/107) of those screened. In the 27 cases that had been diagnosed with a bleeding disorder, 70.3% (19/27) were iron deficient and/or anaemic, and 7.4% or 2 patients required a blood transfusion for anaemia.

In patients with bleeding disorders, hormonal therapies were prescribed in 96% (26/27) of patients. Several patients were treated with more than one treatment modality, simultaneously or consecutively. The combined oral hormonal pill was used in 62% (17/27), Medroxyprogesterone, either orally or in Depot form in 26% (7/27), and LNG-IUS (Mirena, Bayer) in 30% (8/27). Tranexamic acid, an antifibrinolytic agent, was utilised in 87% of all patients with a bleeding disorder. Iron replacement was required in 70% (19/27) of patients. It was uncommon for targeted haemostatic therapies such as Desmopressin and factor concentrates to be required for HMB, and these were prescribed under the supervision of the treating haematologist. Acute surgical management for heavy menstrual bleeding was not required in any case, as all cases were able to be managed with medical management.

Discussion

The findings of this study would suggest that adolescents presenting with HMB, and/or anaemia to a tertiary centre should be further evaluated for a bleeding disorder, including a thorough bleeding and family history and laboratory haemostatic

investigation. Adolescents referred to the paediatric and adolescent gynaecologist are likely to be a higher risk population for bleeding disorders. They are more likely to have had a prior review in the primary care or general gynaecology setting, and may have been non-responsive to usual first line management for HMB. The adolescent with heavy menses and iron deficiency anaemia may be affected by fatigue, be spending less time on enjoyable activities such as sport, absence from school, and be have difficulty concentrating and performing schoolwork. [12] Early diagnosis of a bleeding disorder may assist to reduce morbidity and suffering from HMB in the adolescent period, but importantly it will identify those at increased risk for long term complications such as surgical or obstetric haemorrhage. Published data shows that 8 - 18% of women with a bleeding disorder will proceed to have surgery for HMB, including for management of haemorrhagic ovarian cysts or hysterectomy. An undiagnosed bleeding disorder may pose a greater risk of complications in these women. [13]

Screening

A systematic and stepwise haemostatic evaluation in young women presenting with HMB should be undertaken. A comprehensive bleeding history is critical and should include detailed questioning regarding the presence of abnormal bruising, mucosal bleeding (epistaxis and oral bleeding), post-surgical and post-dental procedure bleeding and bleeding after minor trauma. There is a wide spectrum of minor bleeding reported by healthy individuals and it can be difficult to be definitive around what constitutes a history of 'abnormal bleeding'. Screening tools, such as Pictorial Blood Assessment Charts (PBAC), may be of assistance in quantifying the amount of bleeding the adolescent is experiencing. [14] The use of validated bleeding assessment tools (BATs) are increasingly being used in clinical

Haematology practice to assist in identifying individuals with a bleeding history that is abnormal and predictive of an underlying bleeding disorder. Whilst there are paediatric specific BATs (the Paediatric Bleeding Questionnaire [15, 16] and ISTH-BAT [17]), these BATs still lack sensitivity, efficiency and flexibility in the paediatric and adolescent setting. [18] It should be noted that these younger patients are less likely to have had significant surgical challenges compared to their adult counterparts and therefore (apart from menstruation) have had fewer opportunities for a bleeding disorder to become manifest. The limitations of currently available paediatric BATs are recognised and newer BATs are in development that will hopefully address these deficiencies. [19]

Investigation

Initial laboratory testing as outlined in **Figure 3** should reasonably include a full blood count and examination of the blood film, prothrombin time (PT), activated patient thromboplastic time (APPT), clottable (Clauss) fibrinogen, and von Willebrand screen (including a factor VIII level, VWF:Antigen, VWF:Ristocetin cofactor activity and VWF: Collagen binding assay. An automated platelet function analysis test (PFA-100) may also be considered as part of the general screen. Where a family history of a clotting factor deficiency is present or where the initial screening coagulation profile is abnormal then additional factor levels will be required in consultation with the Haematologist. It should be noted that despite Haemophilia A and B being X-linked recessive disorders, that approximately 20% of female carriers do have reduced factor VIII or IX levels (due to skewed lyonization) and that this can lead to problematic menstrual bleeding. [20]

Where initial testing is normal but the clinical history is suggestive of a bleeding disorder or where HMB is persistent (without other gynaecological or endocrine cause) then more detailed haemostatic investigation is warranted in consultation with the Haematologist. Disorders of platelet function requires specialised platelet aggregometry (+/- electron microscopy and platelet glycoprotein flow cytometry) testing and such investigations can usually only be performed in a tertiary haemostatic laboratory. It is important to note that automated platelet function testing (for example the PFA-100) is not considered diagnostic of a platelet function disorder as it is subject to considerable pre-analytical variables, and abnormal results may be encountered simply due to transport artefact or medication use, particularly non-steroidal anti-inflammatory drugs. The PFA-100 test is also not sensitive to mild disorders of platelet function. [21]

Due to the many pre-analytical variables that can impact on the haemostatic system investigations (particularly VWF levels and platelet aggregometry) it is not uncommon for repeat investigations to be required before a diagnosis can be confirmed. Accurate subclassification of type 2 VWD will also require further specialized testing including a Ristocetin induced platelet aggregation (RIPA) test. [22] The repeated testing to establish a formal diagnosis may prove frustrating for children and their families in some situations.

Diagnosis

The challenge of making an accurate diagnosis of mild type 1 VWD also exists in this group, as mildly reduced VWF levels of 40-50% are a relatively common finding that may well improve with age and are not themselves diagnostic of type 1 VWD. We had incomplete blood group data for our cohort, however it is well described that individuals who are blood group 0 often have VWF levels that are <0.5 U/ml and this laboratory finding may not clearly segregate with a bleeding or family history. [23] There is some controversy in the literature regarding the testing for VWD in patients already on the combined hormonal oral pill. From the best available evidence, it is not necessary to discontinue these to investigate for VWD, as VWF Ag, Factor III, and Ristocetin cofactor parameters are not affecting by combined hormonal pills. [24]

Given the propensity for borderline levels to resolve with age, for patients with borderline low VWF levels it may be more appropriate to use the term “low VWF” rather than labelling a young adolescent with a disease. Patients with low VWF can be considered to have a risk factor for bleeding, rather than a disorder and their bleeding history and VWF levels can be followed up over time as many will never meet the criteria for formal diagnosis of VWD. [8]

We did not diagnose any rarer forms of VWD (type 2 or type 3) in our cohort, likely reflective of both their comparatively lower prevalence and the higher likelihood that these (more severe) disorders would have already become apparent prior to onset of menstruation due to the manifestation of other bleeding symptoms.

Rare factor deficiencies are occasionally found in girls presenting with refractory HMB. Factor II, V and X deficiency would be suspected due to prolongation of both the APTT and PT (see diagram), and factor VII deficiency by prolongation of the PT. It should be noted that mild intrinsic pathway deficiencies (factor VIII, IX, XI) may not always prolong the APTT, and if suspected from the family or clinical history these should be specifically requested. Factor XIII deficiency does not alter the coagulation profile, however it is extremely rare and should only be tested where HMB is occurring in conjunction with other unexplained significant bleeding symptoms. [25]

Management

Institution of appropriate long-term management of menses in adolescents with bleeding disorders will be of considerable benefit in preventing morbidity. With mild bleeding disorders causing chronic heavy menstrual bleeding, the combined oral hormonal pill, progesterone only hormonal options, and antifibrinolytics are considered first-line treatment [26, 27, 28]. In our institution, it would be routine to present all of the hormonal and non-hormonal options, screen for contraindications, and then allow the adolescent and parent/caregiver to make an informed choice after counselling.

Estrogen-containing oral contraceptive medications are effective in reducing the frequency and duration of menstrual periods. Administration of a combined pill containing 30 mcg ethinyl oestradiol diminishes the secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary, thereby inhibiting ovulation and leading to stabilization of the endometrial surface of the uterus [29]. Alternative routes of administration of combined

estrogen and progesterone preparations are transdermal preparations and vaginal rings, however these but not in widespread use in Australia in the adolescent population, and have not been investigated in the adolescent bleeding disorder population.

If there are contraindications to the use of estrogen containing preparations, or patient preference is for a progesterone only method, we would commonly offer either cyclical Medroxyprogesterone acetate 20-40mg oral once daily for 21 days each month, or if the goal is menstrual suppression, Depot Medroxyprogesterone acetate 150mg every 12 weeks. We have found the LNG-IUS to be a highly effective at achieving menstrual suppression in adolescents with bleeding disorders, with 30% of our cohort proceeding to insertion of Mirena IUS. At our institution we would routinely offer this as a treatment modality for all adolescents with HMB, with insertion under GA, as the safety in the adolescent population has been well established. [30]

Tranexamic acid (TEXA) is an anti-fibrinolytic agent that may be used alone or in conjunction with hormones, and is highly effective at reducing menstrual bleeding in patients with bleeding disorders. TEXA was used in up to 87% of adolescents with bleeding disorders in this cohort. It competitively inhibits the activation of plasminogen to plasmin, and at higher concentrations, is a non-competitive inhibitor of plasmin. [31] Typically, TEXA is dosed intermittently for HMB, with our usual protocol being a 15-25mg per kg per dose (maximum 1.5 grams) given orally three times a day, for days 1 to 4 of the menstrual cycle. Aminocaproic acid (Amicar) is an alternative antifibrinolytic, however, it is not currently marketed in Australia. We typically prescribe TEXA in conjunction with progesterone only preparations, such as Medroxyprogesterone or Norethisterone, rather than oestrogen

containing combined pills, as the use of estrogen in addition TEXA, may pose a greater risk of venous thromboembolism.

Acute Haemorrhage

In cases involving acute haemorrhage, hospitalization and/or blood transfusions may be required. It is interesting to note that blood transfusion was required very rarely in our cohort of adolescents with HMB and an underlying bleeding disorder. This may reflect the prompt recognition of iron deficiency and early aggressive management with appropriate iron therapy in our cohort whilst working to control underlying HMB with hormonal and antifibrinolytic therapy. The well-established "restrictive transfusion policy" at our centre may have also contributed to the low blood transfusion rate observed.

There are various hormonal regimes that can be used **(Table 1)**, however the data in the literature specifically comparing the effectiveness of various modalities in specifically in adolescents with bleeding disorders with acute heavy bleeding is limited. Estrogen may be given intravenously, 25mg IV every 4-6 hours, or alternatively in the form of a 30-50 mcg ethinyl oestradiol combined pill 1 tablet every 6 hours, until bleeding ceases, which in most cases occurs within 24 hours of treatment. Alternatively, progesterone only treatments are available and have been shown to be effective. At our institution, for heavy acute bleeding we would commence Medroxyprogesterone acetate 10-20mg every 6 to 8 hours, or Norethisterone 5 -10 mg every 8 hours. Once bleeding has settled, tapering of the hormonal therapies will be required, and there are various protocols regimes for weaning to a maintenance does of hormonal therapies exist [28]. Additionally, in the setting of acute heavy bleeding, tranexamic acid may be given at a dose of 1g by intravenous injection over

10 minutes, followed by oral administration as per protocol described above. Surgical interventions such as dilatation and curettage, and or insertion of 30cc Foley Catheter balloon is only very rarely required when prompt medical management is instituted.

Targeted therapy

Accurate and early recognition of bleeding disorders in the adolescent is critical for management of future severe bleeding episodes that may benefit from directed therapies, preoperative prophylaxis and treatment of surgical haemorrhage, including future preparation for obstetric related bleeding. For patients with mild to moderate VWD type 1, mild haemophilia A, some patients with type 2A and type 2M VWD and some mild platelet function disorders, Desmopressin (a synthetic vasopressin analogue) can be used. In Australia this is available in subcutaneous and intravenous preparations, and in some countries, in nasal preparations. Desmopressin stimulates the release of endothelial VWF, thereby increasing the levels of VWF, and enhancing platelet adhesion to the vessel wall. [32] Desmopressin is generally reserved for refractory HMB that has not responded to anti-fibrinolytic and multiple hormonal approaches. Caution with fluid restriction to two-thirds maintenance for 24 hours after each dose is imperative to prevent hyponatremia. [33] Severe forms of VWD require clotting factor concentrates containing VWF for treatment (or rarely prevention) of haemorrhages.

Iron replacement

Iron deficiency and/or anaemia contributes to morbidity seen in this population, and this study has demonstrated a high prevalence of iron deficiency and/or anaemia. Adolescents with heavy menstrual bleeding should therefore be screened for iron deficiency anaemia, and appropriate treatment instituted. It is very important to be very specific when prescribing oral iron replacement as there exist many over the counter supplements which have very low content of iron and provide little benefit (**Table 2**). We routinely recommend a combined iron formulation such as Ferrograd C containing ferrous sulfate 325mg (equivalent to 105mg of elemental iron) and Sodium ascorbate (equivalent to 500mg or ascorbic acid or Vitamin C) for improved absorption, at a dose of one tablet daily. The availability of newer, safer, more cost effective intravenous iron preparations (iron carboxymaltose, Ferinject) and generally unfavourable side effect profile of oral preparations may lower the threshold for replacing iron intravenously. Ferinject is given at a maximum single dose of up to 1000mg as an intravenous infusion over 15 minutes, which may be repeated a week later, according to the Ganzoni formula. [34]

Limitations and Strengths

The retrospective nature of this cohort study meant that HMB was not able to be objectively measured, which is a limitation encountered by other groups investigating HMB and reflects the challenges in trying to design and carry out prospective studies in the field of adolescent menstruation. The research was carried out in a tertiary care centre and by virtue of a referral pattern reflecting more refractory cases of HMB, it is almost certain that the prevalence of bleeding disorders in the population has been overestimated compared to that seen in studies from a primary care setting. A strength of this study is that all patients

were reviewed and classified according to standardized criteria by a specialist Paediatric Haematologist.

Conclusion

Our data is consistent with international published literature that shows that a large proportion of adolescent girls with HMB referred to a tertiary PAG clinic will have an underlying bleeding disorder. It is likely that a high proportion of adolescents with HMB presenting in the primary setting may also be underrecognized and untreated, and thus there should be a low threshold to recognise, screen and treat.

These findings support comprehensive and systematic haemostatic evaluation in adolescents with HMB. A higher level of awareness of bleeding disorders as a cause for HMB in adolescence, especially VWD and platelet function disorders, is needed and close multidisciplinary collaboration between the paediatric and adolescent gynaecologist and haematologist in a specialised tertiary centre should be established in the management of these patients. Effective management can be accomplished with either hormonal medications alone or in conjunction with antifibrinolytic agents in the majority of patients. In adolescents who are already known to have a bleeding disorder, consultation with a paediatric gynaecologist and/or haematologist prior to menarche may be helpful to outline abnormal patterns of menstrual bleeding and to discuss options of treatment in the event of HMB.

Disclosure/Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

References

1. Friberg B, Orno AK, Lindgren A, Lethagen S: Bleeding disorders among young women: a population-based prevalence study. *Acta Obstet Gynecol Scand* 2006; 85: p. 200.
2. Ahuja SP, Hertweck SP: Overview of bleeding disorders in adolescent females with menorrhagia. *J Pediatr Adolesc Gynecol* 2010; 23(6 Suppl.): S15–21.
3. Chi C, Pollard D, Tuddenham EG, et al: Menorrhagia in adolescents with inherited bleeding disorders. *J Pediatr Adolesc Gynecol* 2010; 23: p. 215.
4. Vo KT, Grooms L, Klima J, et al: Menstrual bleeding patterns and prevalence of bleeding disorders in a multidisciplinary adolescent haematology clinic. *Haemophilia* 2013; 19: p. 71.
5. Mills HL, Abdel-Baki MS, Teruya J, Dietrich JE, Shah MD, Mahoney D, Yee DL, Srivaths LV: Platelet function defects in adolescents with heavy menstrual bleeding. *Haemophilia* 2014; 20 (2): p. 249.
6. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA: Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet* 1998; 14: 351: p. 485.
7. Lavin M, Aguila S, Schneppenheim S, Dalton N, Jones KL, O'Sullivan JM, O'Connell NM, et al. Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels. *Blood* 2017. 130(21): p. 2344-2353.
8. Sadler JE. Von Willebrand disease type 1: a diagnosis in search of a disease. *Blood* 2003. 101(6): p. 2089-93.
9. Laffan MA, Lester W, O'Donnell JS, Will A, Tait RC, Goodeve A, Millar CM, Keeling DM. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol* 2014. 167(4): p. 453-65.

10. Gresele P. Diagnosis of inherited platelet function disorders: guidance from the SSC of the ISTH. *J Thromb Haemost* 2015. 13(2): p. 314-22.

11. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlan CA, et al. Guidelines for the management of hemophilia. *Haemophilia* 2013. 19(1): p. e1-47.

12. Wang W, Bourgeois T, Klima J, et al: Iron deficiency and fatigue in adolescent females with heavy menstrual bleeding. *Haemophilia* 2012; 19:225.

13. James AH. More than menorrhagia: a review of the obstetric and gynaecological manifestations of bleeding disorders. *Haemophilia* 2005; 11: 295.

14. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990; 97: 734–9.

15. Bidlingmaier C, Grote V, Budde U, Olivieri M, Kurnik K. Prospective evaluation of a pediatric bleeding questionnaire and the ISTH bleeding assessment tool in children and parents in routine clinical practice. *J Thromb Haemost* 2012. 10(7): p. 1335-41.

16. Bowman M, Riddel J, Rand ML, Tosetto A, Silva M, James PD. Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost* 2009. 7(8): p. 1418-21.

17. Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Coller B, James P, Neunert C, Lillicrap D. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost* 2010. 8(9): p. 2063-5.

18. Rydz N, James PD. The evolution and value of bleeding assessment tools. *J Thromb Haemost* 2012. 10(11): p. 2223-9.

19. Stokhuijzen E, Rand ML, Cnossen MH, Biss TT, James PD, Suijker MH, Peters M, et al. Identifying Children with Hereditary Coagulation disorders (iCHEC): a protocol for a prospective cohort study. *BMJ Open* 2018. 8(5): p. e020686.
20. Boban A, Lambert C, Lannoy N, Hermans C. Comparative study of the prevalence of clotting factor deficiency in carriers of haemophilia A and haemophilia B. *Haemophilia* 2017. 23(5): p. e471-e473.
21. Harrison P, Mackie I, Mumford A, Briggs C, Liesner R, Winter M, Machin S. Guidelines for the laboratory investigation of heritable disorders of platelet function. *Br J Haematol* 2011. 155(1): p. 30-44.
22. Frontroth JP, Favaloro EJ. Ristocetin-Induced Platelet Aggregation (RIPA) and RIPA Mixing Studies. *Methods Mol Biol* 2017. 1646: p. 473-494.
23. Albanez S, Ogiwara K, Michels A, Hopman W, Grabell J, James P, Lillicrap D. Aging and ABO blood type influence von Willebrand factor and factor VIII levels through interrelated mechanisms. *J Thromb Haemost* 2016. 14(5): p. 953-63.
24. Dumont T, Allen L, Kives S. Can von Willebrand Disease Be Investigated on Combined Hormal Contraceptives? *J Pediatr Adolesc Gynecol* 2013. 26 (3): p. 138-41.
25. Bolton-Maggs PH. The rare inherited coagulation disorders. *Pediatr Blood Cancer* 2013. 60 Suppl 1: p. S37-40.
26. Alaqzam TS, Stanley AC, Simpson PM, Flood VH, Menon S. Treatment Modalities in Adolescents Who Present with Heavy Menstrual Bleeding. *J Pediatr Adolesc Gynecol* 2018. 31(5): p. 451-458.
27. Powers JM, Stanek JR, Srivaths L, Haamid FW, O'Brien SH. Hematological Considerations and Management of Adolescent Girls with Heavy Menstrual Bleeding and Anemia in US Children's Hospitals. *J Pediatr Adolesc Gynecol* 2018. 31(5): p. 247-250.

28. Haamid F, Sass AE, Dietrich JE. Heavy Menstrual Bleeding in Adolescents. NASPAG Committee Opinion. *J Pediatr Adolesc Gynecol* 2017. 30(3): p. 335-340.

29. Reproductive Endocrinology. In: Hoffman B, Schorge J, Bradshaw K, Halvorson L, Schaffer J, Corton M. Williams Gynaecology. 2016 3e, New York, NY: McGraw-Hill, Section 2, Chapter 17; Section ID 118170024. Accessed August 22, 2018.

30. Adeyemi-Fowode OA, Santos XM, Dietrich JE, SrivathL. Levonorgestrel-Releasing Intrauterine Device Use in Female Adolescents with Heavy Menstrual Bleeding and Bleeding Disorders: Single Institution Review. *J Pediatr Adolesc Gynecol* 2017. 30(4): p479-483.

31. Bryant-Smith A, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev, 2018. 4: p. CD000249.

32. Leissinger C, Carcao M, Gill JC, Journeycake J, Singleton T, Valentino L. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. *Haemophilia* 2014. 20(2): p. 158-67.

33. Mason JA, Robertson JD, McCosker J, Williams BA, Brown SA. Assessment and validation of a defined fluid restriction protocol in the use of subcutaneous desmopressin for children with inherited bleeding disorders. *Haemophilia* 2016. 22(5): p. 700-5.

34. Baird-Gunning J, Bromley J. Correcting iron deficiency. *Aust Prescr* 2016. 39(6): p.193-199.

Table 1: Medical and hormonal Therapies for Acute Heavy Menstrual bleeding

Therapy	**Dose**	**Route**	**Initial Frequency**
Conjugated oestrogen	25 mg	IV	Every 4 -6 hours
50 mcg ethinyl oestradiol combined pill	1 tablet	Oral	Every 6 hours
30 mcg ethinyl oestradiol combined pill	1 tablet	Oral	Every 6 hours
Medroxyprogesterone	10-20mg	Oral	Every 6 to 8 hours
Norethisterone	5-10mg	Oral	Every 8 hours
Tranexamic acid	1g	Intravenous	One dose over 10 minutes
Tranexamic acid	15-25mg per kg per dose (max 1.5 g)	Oral	Every 8 hours

Table 2: Commonly available Oral Iron preparations

Brand name	**Formulation**	**Elemental Iron content**
Ferro-gradumet	Ferrous sulfate 325mg Controlled-release tablets	105mg
Ferrograd C	Ferrous sulfate 325mg Vitamin C 500mg Controlled-release tablets	105mg
Ferro-tab	Ferrous fumarate 200mg	65.7mg
Ferro-liquid	Ferrous Sulfate 30mg/ml	6mg/ml

Figure 1: Prevalence of Bleeding Disorders in patients with Heavy Menstrual Bleeding Presenting to Queensland PAG Service.

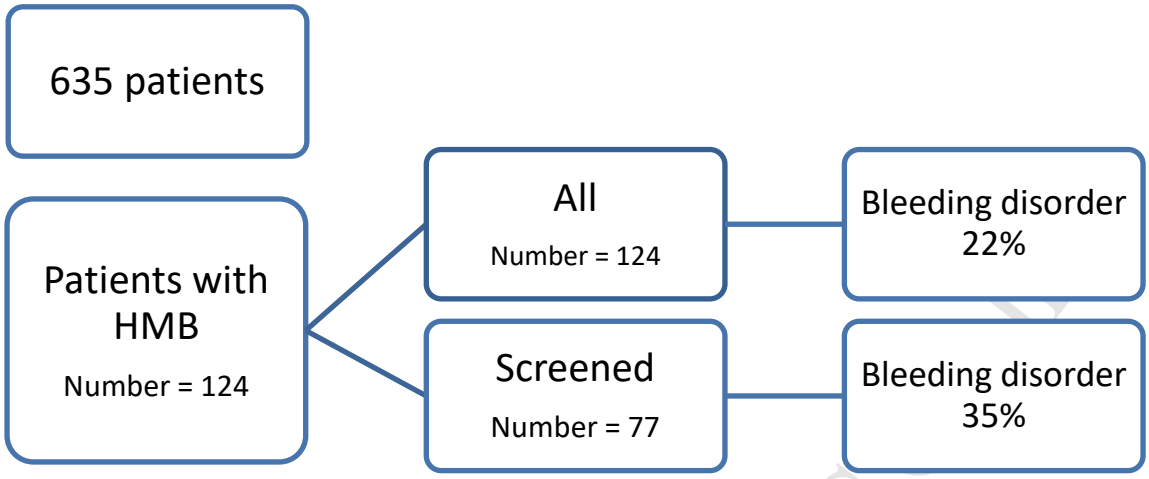


Figure 2: Classification of Bleeding Disorders in Adolescents with HMB.

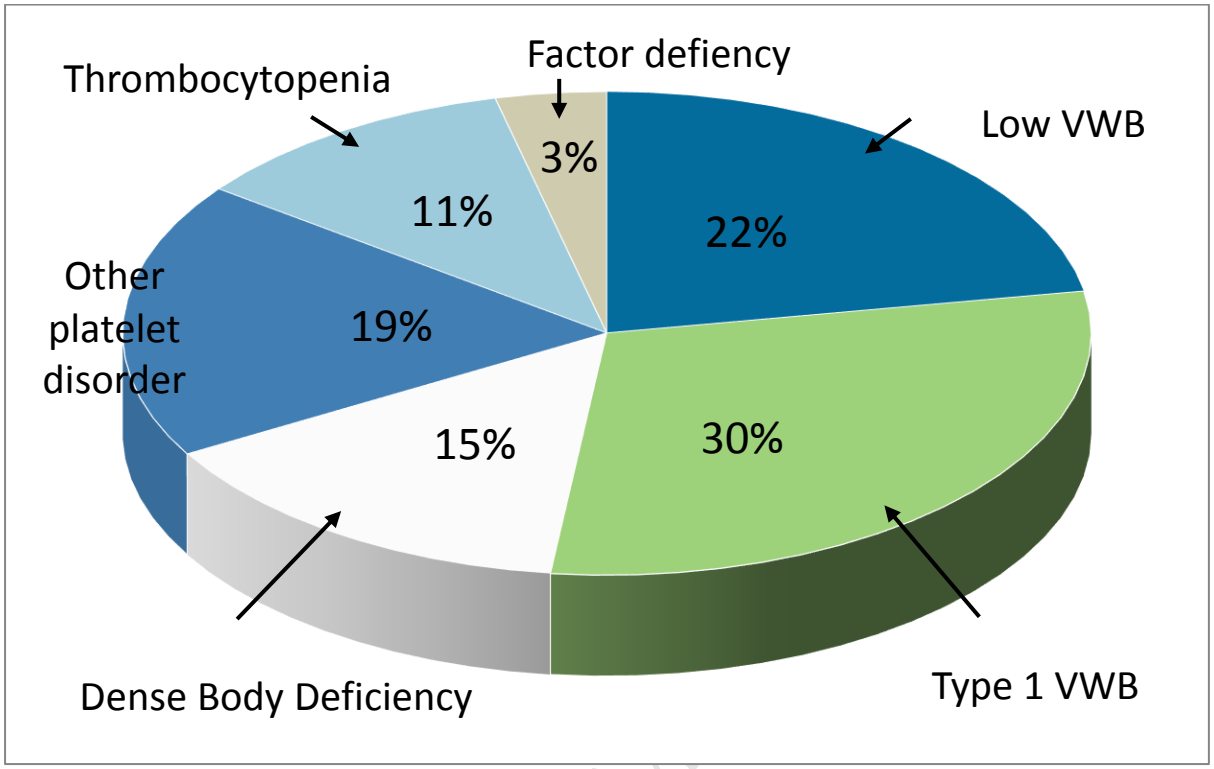


Figure 3: Tiered approach to the laboratory Investigation of Adolescents with HMB